Aus der

Klinik und Poliklinik für Strahlentherapie und Radioonkologie

Klinikum der Ludwig-Maximilians-Universität München

Hypofraktionierung in der Strahlentherapie des anaplastischen Schilddrüsenkarzinoms

Dissertation

zum Erwerb des Doktorgrades der Medizin

an der Medizinischen Fakultät

der Ludwig-Maximilians-Universität München

vorgelegt von

Dmytro Oliinyk

aus

Chernivtsi

Jahr

2024

Meiner Familie

Mit Genehmigung der Medizinischen Fakultät der

Ludwig-Maximilians-Universität zu München

Erster Gutachter:	Prof. Dr. med. Claus Belka
Zweiter Gutachter:	Prof. Dr. med. Christine Spitzweg
Dritter Gutachter:	Prof. Dr. med. Vera Wenter
Dekan:	Prof. Dr. med. Thomas Gudermann

Tag der mündlichen Prüfung: 13.09.2024

Affidavit

LMU LUDWIG-MAXIMILIANS-UNIVERSITÄT MÜNCHEN

Promotionsbüro Medizinische Fakultät

MMRS

Eidesstattliche Versicherung

Oliinyk, Dmytro
Name, Vorname

Ich erkläre hiermit an Eides statt, dass ich die vorliegende Dissertation mit dem Titel:

Hypofraktionierung in der Strahlentherapie des anaplastischen Schilddrüsenkarzinoms

selbstständig verfasst, mich außer der angegebenen keiner weiteren Hilfsmittel bedient und alle Erkenntnisse, die aus dem Schrifttum ganz oder annähernd übernommen sind, als solche kenntlich gemacht und nach ihrer Herkunft unter Bezeichnung der Fundstelle einzeln nachgewiesen habe.

Ich erkläre des Weiteren, dass die hier vorgelegte Dissertation nicht in gleicher oder in ähnlicher Form bei einer anderen Stelle zur Erlangung eines akademischen Grades eingereicht wurde.

Regensburg, 13. September 2024. Dmytro Oliinyk

Ort, Datum

Unterschrift Doktorandin bzw. Doktorand

Inhaltsverzeichnis

Abkürzungsverzeichnis

ALK - Anaplastic lymphoma kinase

ATA – American Thyroid Association

ATC – Anaplastic thyroid carcinoma (anaplastisches Schilddrüsenkarzinom)

BRAF – Proto-oncogene B-Raf oder v-Raf murine sarcoma viral oncogene homolog B1

V600E – BRAF-Mutation mit Valin (v) anstelle von Glutaminsäure (e) an der Position 600

ChT – Chemotherapie

CI – Confidence interval (Konfidenzintervall)

CR – Complete response

CT – Computertomographie

CTCAE - Common Terminology Criteria for Adverse Events

DSS – Disease-specific survival (krankheitsspezifisches Überleben)

DTC – Differentiated thyroid carcinoma (differenziertes Schilddrüsenkarzinom)

ECOG-Score – Perfomance score gemäß Eastern Cooperative Oncology Group

EMA – Epithelial membrane antigen

EQD2 – eqivalent dose in 2-Gy fractions (Äquivalentdosis in 2-Gy-Fraktionen)

ESMO – European Society for Medical Oncology

FAP – Familial adenomatous polyposis

FDA – Food and Drug Administration

FDG-PET-CT – ^{18}Fluor-Desoxyglukose Positronen-Emissions-Tomographie und CT

FNA – Feinnadelaspirationszytologie

FTC – Follicular thyroid carcinoma (follikuläres Schilddrüsenkarzinom)

Gy – Gray

HR – Hazard ratio

Ki67 – Kiel-Antigen Nr. 67

KPS – Karnofsky Performance Score

LC – Local control (lokale Kontrolle)

MEK – Mitogen-activated protein kinase

MTC – Medullary thyroid carcinoma (medulläres Schilddrüsenkarzinom)

mTOR – Mammalian target of rapamycin

NCCN – National Comprehensive Cancer Network

NCT – National clinical trial

NGS – Next generation sequencing

NTRK – Neurotrophic tyrosine receptor kinase

OR – Odds ratio

ORR – Overall response rate - Gesamtansprechrate

OS – Overall survival (Gesamtüberleben)

p21 – Cyclin-dependent kinase Inhibitor 1

PAX8 – Paired-box protein 8

PD(L)-1 – Programmed cell death protein 1 (ligand)

PDTC – Poorly differentiated thyroid carcinoma (schlecht- bzw. wenig-differenziertes Schilddrüsenkarzinom)

PFS – Progression-free survival (progressionsfreies Überleben)

PI3KCA – Phosphatidylinositol 3-kinase

PPRγ – Peroxisome proliferator-activated receptor gamma

PR – Partial response

PSM – Propensity score matching

PTC – Papillary thyroid carcinoma (papilläres Schilddrüsenkarzinom)

R-Status – Resektionsausmaß eines Tumors nach TNM-Klassifikation (R0 – mikroskopisch tumorfrei, R1 – makroskopisch tumorfrei, R2 – makroskopische Tumorreste)

RET – Rezeptortyrosinkinase Ret - rearranged during transfection

RET/PTC – Rearranged during transfection/papillary thyroid carcinoma Fusionsprotein

RT – Radiotherapie

SD – Stable disease

SEER - Surveillance, Epidemiology, and End Results Program

TC – Thyroid cancer (Schilddrüsenkarzinom)

TERT – Telomerase reverse transcriptase

TNM – Facetten-Klassifikation der Ausdehnung des Primärtumors (T), Lymphknotenbefalls (N) und Metastasen (M)

TP53 – Tumorsuppressorprotein p53

TPS – Tumor proportion score

TSH – Thyreoidea-stimulierendes Hormon

TTF-1 – Thyroid transcription factor 1

UICC – Union internationale contre le cancer

Publikationsliste

Publikation I (Erstautorenschaft): Hypofractionated Radiotherapy for Anaplastic Thyroid Cancer: Systematic Review and Pooled Analysis

Journal: Cancers

Impact factor (2020): 6.639

Publikation II (Koautorenschaft): Clinical Outcome and Toxicity in the Treatment of Anaplastic Thyroid Cancer in Elderly Patients

Journal: Journal of Clinical Medicine

Impact factor (2020): 4.242

Publikation III (Koautorenschaft): Radiation to the Primary Tumor in Metastatic Anaplastic Thyroid Cancer

Journal: In vivo

Impact factor (2019*): 1.541

**bekannter JIF zum Zeitpunkt des Einreichens der Publikation*

Impact factor (2020): 2.155

Publikation IV (Erstautorenschaft): Role of surgery to the primary tumor in metastatic anaplastic thyroid carcinoma: pooled analysis and SEER-based study

Journal: Journal of Cancer Research and Clinical Oncology

Impact factor (2021): 4.322

1. Der jeweils eigene Beitrag zu den Veröffentlichungen

1.1 Der Beitrag zur Publikation I

Diese Publikation wurde nahezu vollständig von mir konzipiert und erstellt. Dabei beschäftigte ich mich vor allem mit der Formulierung der Hypothese, der Datenerhebung und der schriftlichen Darstellung, wobei ich von der Koautorin Teresa Augustin unterstützt wurde. Die Arbeit und die Publikation wurde von mir und meinem Koautor Dr. Lukas Käsmann geplant. Die erhobenen Daten wurden von mir interpretiert und ausgewertet. Von der Koautorin Teresa Augustin und dem Koautor Dr. Lukas Käsmann unterstützen wurde ich dabei bei der Diskussion der statistischen Ergebnisse unterstützt. Unter Supervision von Prof. Dr. Claus Belka, Prof. Dr. Christine Spitzweg, Dr. Viktoria Köhler, Dr. Josefine Rauch und Dr. Lukas Käsmann wurde von mir auch das Manuskript erstellt. Der Koautor Prof. Claus Belka und die Koautorin Prof. Christine Spitzweg unterstützten mich dabei u. a. bei der Ausarbeitung der Diskussion und bei der Gestaltung des Artikeldesigns. Als korrespondierender Koautor fungierte Dr. Lukas Käsmann und die Revision der Publikation vor der Veröffentlichung wurde von mir durchgeführt. Am Lektorat waren alle Autoren beteiligt.

1.2 Der Beitrag zur Publikation II

Diese Publikation wurde vor allem von Teresa Augustin konzipiert und erstellt. Auch die Auswahl und Anwendung der Methoden und die Koordinierung bei der Umsetzung der Methoden wurden von Teresa Augustin übernommen. Die Supervision wurde von Prof. Dr. Claus Belka, Prof. Dr. Christine Spitzweg und Dr. Lukas Käsmann durchgeführt. Mein Beitrag beschränkte sich auf eine Unterstützung der Erstautorin bei der Datenakquise und -auswertung, bei der Redaktion der Tabellen und Schemata und bei der Erstellung und Anpassung des Manuskripts.

1.3 Der Beitrag zur Publikation III

Auch die Publikation III wurde hauptsächlich von Teresa Augustin konzipiert und erstellt. Die Erstautorin beschäftigte sich dabei insbesondere mit der Entwicklung der Hypothese und der Planung und Umsetzung der Arbeit. Als Koautor war ich an der Akquise der Patientendaten aus unserem Zentrum, der Vorbereitung der statistischen Auswertung, der Auswertung der Daten und der Anpassung und Erstellung des Manuskripts beteiligt. Die Supervision der Arbeit wurde von Prof. Dr. Claus Belka, Prof. Dr. Christine Spitzweg, Dr. Josefine Rauch und Dr. Lukas Käsmann übernommen.

1.4 Der Beitrag zur Publikation IV

Als Erstautor der Publikation IV war ich für die Erstellung der Hypothese, die Planung der Arbeit und die Auswahl der Methoden, die Koordination und statistische Aufbereitung und die Erstellung des Manuskripts verantwortlich. Der für die Arbeit erforderliche Zugang zur SEER-Database wurde durch den Koautor Dr. Lukas Käsmann ermöglicht. Die Koautoren Prof. Dr. Claus Belka, Prof. Dr. Christine Spitzweg, Dr. Viktoria Köhler und Dr. Josefine Rauch unterstützten mich mit

ihrer fachlichen Expertise bei der Revision des Manuskripts, der Planung der Diskussion und der Auswertung der Daten. Für die Korrespondenz mit dem Journal war Dr. Lukas Käsmann verantwortlich, die Revision und das Proof-Reading wurden hauptsächlich von mir und Teresa Augustin durchgeführt. Das Lektorat übernahmen alle Autoren.

2. Einleitung

2.1 Epidemiologie

Das anaplastische Schilddrüsenkarzinom (anaplastic thyroid cancer, ATC) bildet mit einer Prävalenz von ca. 2-3 % aller bösartigen Schilddrüsenneubildungen eines der seltensten Malignome [1–3]. Geographisch und auch geschlechtsspezifisch zeigen sich dabei deutliche Unterschiede [1–3]. Weltweit konnte in den letzten Jahren eine steigende Inzidenz festgestellt werden [1–3]. In Europa lag der Anteil des ATCs an allen Schilddrüsenmalignitäten im Zeitraum 2000-2007 bei ca. 3 % [4]. Nach dem Zentrum für Krebsregisterdaten des Robert-Koch Instituts erkrankten 2018 in Deutschland 4270 Frauen und 1930 Männer an malignen Schilddrüsentumoren [5]. Die Prognose beim ATC bleibt mit einem medianen Überleben von 3-6 Monaten und einer 1- bzw. 10-Jahresüberlebensrate von ca. 10-20 % bzw. < 5 % infaust [6,7]. Deshalb ist bei der insgesamt guten Prognose der differenzierten Schilddrüsenkarzinome das ATC für einen beträchtlichen Anteil der Sterbefälle verantwortlich [6,7].

2.2 Grundlagen

Schilddrüsenkarzinome (thyroid cancer, TC) werden histologisch hinsichtlich ihres Differenzierungsgrades unterteilt [8]. Papilläre und follikuläre TC und das Hürthe-Zell Karzinom gehören zu den differenzierten Schilddrüsenkarzinomen (*differentiated thyroid cancer*, DTC) [8]. Das ATC bildet eine undifferenzierte Unterform [8]. Außerdem gibt es noch schlecht differenzierte Karzinome (*poorly differentiated thyroid cancer*, PDTC) und das medulläre Schilddrüsenkarzinom, das von den C-Zellen ausgehend eine Sonderstellung einnimmt (*medullary thyroid cancer*, MTC) [8]. DTCs sind mit ca. 85-90 % und einer 10-Jahresüberlebensrate von über 95 % für die meisten Neuerkrankungen verantwortlich [9–13]. Die genauen ätiologischen Faktoren, die zur Entwicklung eines ATCs beitragen könnten, sind bis auf bereits vorhandene DTC-Läsionen oder Struma weitgehend unbekannt [14,15]. Die wichtigsten Risikofaktoren für die Entwicklung eines DTCs sind nach wie vor eine Exposition gegenüber radioaktiver Strahlung, Hashimoto Thyreoiditis, familiäre adenomatöse Polyposis (FAP) und das Cowdens-Syndrom [16–20].

Pathophysiologisch wurden für TCs zwei Hypothesen für die Karzinogenese aufgestellt, nämlich die klonale Evolution und das Stammzellmodell [21]. Dabei wird verdeutlicht, dass ATCs sowohl sekundär aus DTCs als auch *de novo* entstehen können. Bei der ersten Hypothese, der klonalen Evolution, wird der kumulative Effekt stochastischer Mutationen verantwortlich gemacht [21,22]. So wurde etwa beim Auftreten sequenzieller Mutationen im Tumorsuppressorprotein p53-Gen (*TP53*) und im *cyclin-dependent kinase inhibitor-1*-Gen (*p21*) für follikuläre Schilddrüsenkarzinome (follicular thyroid carcinoma, FTC) und papilläre Schilddrüsenkarzinome (papillary thyroid carcinoma, PTC) eine mögliche Transformation in ATC, und zwar teilweise über schlecht-differenzierte Schilddrüsenkarzinome als Zwischenstadium beschrieben [21–25]. Die zweite Hypothese des Stammzellmodels beschreibt die fehlende Konkordanz der für DTCs typischen Alterationen von Fusionsproteinen *rearranged during transfection/papillary thyroid carcinoma* (*RET/PTC*) und *paired-box protein 8/peroxisome proliferator-activated receptor gamma* (*PAX8/PPRγ*) bei ATCs zu erklären [21,26]. In diesem Fall werden neben genetischen auch epigenetische Effekte hinsichtlich der Vorläufer der Thyreozyten angenommen [21,22,24]. Beim ATC haben Alterationen im *proto-oncogene B-raf (BRAF*-Gen), inklusive Promotor der *telomerase reverse transcriptase* (*TERT*-Promotor) und den *TP53*- und Phosphatidylinositol-3-Kinase-Genen

(*PI3KCA*) die höchste Prävalenz, wobei durch integrative Transkriptomanalysen auch eine signifikante Hochregulierung im Signalweg *mammalian target of rapamycin* (*mTOR*-Signalweg) nachgewiesen werden konnte [27,28]. Dies findet seine Anwendung auch bei der Immuntherapie des ATCs [29,30]. Dabei zeigt sich beim ATC eine ausgeprägte genomische Heterogenität innerhalb von unterschiedlichen Zelllinien, sodass unter anderem 4 Mutations-Cluster identifiziert wurden [31,32]. Das ausgesprochen aggressive und invasive Wachstum der ATCs kann durch die Wechselwirkungen zwischen den entstehenden Mutationen, genomischer Instabilität und z. T. auch der alterierten Tumormikroumgebung erklärt werden [33–35]. In diesem Zusammenhang werden oft Indices vom Kiel-Antigen Nr. 67 (Ki-67-Indices) > 30 % und hohe Mitoseraten beobachtet [33–35].

Typische gemeinsame Charakteristika für die pathologische Beurteilung des ATCs sind Hyperzellularität mit teilweise den Osteoklasten ähnlichen und mehrkernigen Riesenzellen oder Spindelzellen, zentrale Nekrosen und ein invasives Wachstumsmuster insbesondere in den naheliegenden Gefäßen, was ein wichtiges Unterscheidungsmerkmal gegenüber den DTCs bildet [8,36]. Generell werden in Abhängigkeit von der Morphologie zwei histologische Hauptkategorien unterschieden: sarkomatoid und epithelial-squamös [36,37]. Daraus ergibt sich eine alternierende immunohistochemische Positivität für Calcitonin, epitheliales Membranantigen (EMA), *paired-box protein 8* (PAX-8), Vimentin und Zytokeratine, wobei das Tumorgewebe nur selten für Thyreoglobuline und den Thyroidalen Transkriptionsfaktor 1 (TTF-1) positiv zu sein scheint [36,38,39].

Die angesprochene Invasivität des Wachstums zeigt sich vor allem durch die in den bei der Diagnosestellung häufig vorhandenen Fernmetastasen und die Infiltration des umliegenden Gewebes [4,40–42]. Deshalb gehören zu den lokalen Komplikationen beim ATC in bis zu 40 % der Fälle vor allem eine Lymphknoteninfiltration, eine Kompression bzw. Infiltration der Trachea mit Dyspnoe und/oder Stridor, eine Kompression bzw. Infiltration des Ösophagus mit Dysphagie, Gefäßnervenschäden und Heiserkeit [43–45]. Die Trachealinfiltration mit sukzessiver Obstruktion der Atemwege bleibt trotz der oft vorhandenen Tracheostomie auch eine der häufigsten tumorbezogenen Todesursachen bei ATC-Patienten (ca. 50 %) [46]. Häufige Manifestationsorte der Fernmetastasen sind Lunge, Mediastinum, Leber und Knochen mit jeweils ca. 25 %, 25 %, 10 % und 6 % der Fälle [47]. Das Vorhandensein der Lymphknoteninvasion oder der angesprochenen Fernmetastasen korreliert neben Tumorgröße, Alter und bestimmten Therapiemodalitäten invers mit dem Gesamtüberleben [40,43,45,48–50].

Deshalb bleibt die initial diagnostische Erfassung der Tumorausbreitung unerlässlich [29, 35]. Die Diagnosestellung beim ATC umfasst neben der Anamnese, der klinischen Untersuchung und dem Labor mit Differentialblutbild und Konzentrationsbestimmung des Thyreoidea-stimulierenden Hormons (TSH) auch einen Halsultraschall, eine Laryngoskopie zur Evaluation der Stimmbandfunktion und eine Computertomographie (CT) von Kopf, Hals, Thorax, Abdomen und Becken mit Kontrastmittel [51]. Bei einer Invasion der Trachea sollte eine Bronchoskopie und ggf. eine Tracheostoma-Anlage durchgeführt werden [51]. Außerdem bleibt eine ^{18}Fluor-Desoxyglukose Positronen-Emissions-Tomographie und CT (FDG-PET-CT) nach wie vor die sensitivste Methode, um die Tumorausbreitung erfassen zu können [29,35,51–54]. Die Diagnose wird vor allem histopathologisch durch eine Feinnadelaspirationszytologie (FNA) oder Stanz-Vakuumbiopsie bestätigt, wodurch ATCs bereits präoperativ von pleomorphen Sarkomen oder Lymphomen unterschieden werden können [29,35,51]. Wegen der zytologisch oft schwierigen Diagnose eines ATCs und der vom Untersucher abhängigen Treffsicherheit bei FNA bleibt eine stereotaktisch geführte Stanz- oder Vakuumbiopsie die Methode der Wahl [29,35,55,56]. Eine molekulare Diagnostik v.a. im Hinblick auf „druggable mutations“ beim ATC wird bei der Diagnosestellung von

den Leitlinien sowohl der *American Thyroid Association* Leitlinien (ATA) als der *European Society for Medical Oncology* (ESMO) und seit 2021/2022 auch des *National Comprehensive Cancer Network* (NCCN) empfohlen [29,35,51,57].

Nach der *Union internationale contre le cancer* (UICC) Version 8 der TNM wird jedes ATC unabhängig von einer lokalen oder disseminierten Tumorausbreitung dem Stadium IVA bis IVC zugeordnet [58]. Neuerdings wird ATC in der aktuellen TNM-Version allerdings nicht mehr standardmäßig mit dem Stadium cT4 verknüpft [58]. Nach der Definition wird aber jedes metastasierte ATC als ein Stadium IVC behandelt [58].

2.3 Die stadiengerechte Therapie beim ATC

Entscheidend für die Therapie ist beim ATC die initiale Tumorausbreitung hinsichtlich einer lokoregionären (UICC-Stadien IVA-B) oder disseminierten Erkrankung (UICC-Stadium IVC) [29,35,51,58]. Im Rahmen einer interdisziplinären Therapieplanung und einer individuellen Risiko-Nutzen-Abwägung werden standardmäßig eine totale Thyroidektomie mit einer anzustrebender R0/R1-Resektion und eine therapeutische und bilateral-zentrale Lymphknoten-Dissektion sowie eine adjuvante Radiochemotherapie empfohlen [51]. Zu einem kleineren Anteil (bis zu 6 %) kommen ATCs auch als Inzidentalome im resezierten Schilddrüsengewebe vor [35]. In solchen Fällen kann sich die Operation auf eine Hemithyroidektomie beschränken, insbesondere wenn eine R0-Resektion durchgeführt wurde, wobei die Entscheidung für eine ergänzende totale Thyroidektomie auf den Merkmalen des nicht-ATC-Bestandteils der Malignität basiert [35]. Die Evidenz für eine weitere Therapie bleibt in solchen Situationen eingeschränkt [35]. Das Ausmaß der Resektion kann bei einer Infiltration des umliegenden Gewebes um eine Laryngektomie oder Ösophagektomie mit einer Muskel- und Gefäßresektion erweitert werden [59]. Weil diese Eingriffe allerdings mit einer erhöhten Morbidität in Verbindung gebracht werden, werden sie auch nicht empfohlen [35,59]. Darüber hinaus wird auch von R2-Resektionen abgeraten, da sich diese als „debulking“ bezeichneten chirurgischen Verfahren nicht als signifikant prognoseverbessernd für ATC-Patienten erwiesen haben [29,35]. Im Unterschied dazu waren R0/R1 in einigen Studien mit einem verbesserten Überleben assoziiert, wobei insbesondere im frühen Stadium IVA eine Morbiditätsreduktion festgestellt wurde [45,59–62]. Der generelle Nutzen einer chirurgischen Resektion konnte bei der lokoregionären Tumorausbreitung durch Studien umfassend belegt werden [40,45,63–70].

Bei R0/R1 resezierten Tumoren werden im kurativen Setting eine adjuvante Bestrahlung mit oder ohne Strahlungssensibilisatoren i.S. einer simultanen Chemotherapie mit hauptsächlich Taxanen und Anthrazyklinen (Daunorubicin, Paclitaxel) und Kombinationen untereinander oder abhängig von der Tumorausbreitung auch mit Platin-Agenten durchgeführt [29,35,51,57]. Bei einer initial nur unvollständig möglichen Resektion kann nach einer entsprechenden Patientenselektion eine neoadjuvante Radio(chemo)therapie angeboten werden [35,51,71–73]. Eine alternative Teilbestrahlung vor der Operation und eine Komplettierung der Bestrahlung nach dem Eingriff können zu einem ähnlichen therapeutischen Nutzen führen wie eine adjuvante Therapie, stellen aber keinen Therapiestandard dar [35,74].

Eine zunehmende Bedeutung erlangt beim ATC die Molekulardiagnostik (*next generation sequencing*, NGS) und zwar insbesondere bei den nicht *in sano* resezierbaren Primärtumoren und im Stadium IVC beim Vorhandensein von Fernmetastasen [29,35,51]. Im Mai 2018 wurde von der *Food and Drug Administration* (FDA) eine Kombinationstherapie für ATC-Patienten mit *BRAF*- und *mitogen-activated protein kinase* Inhibitoren (*MEK*-Inhibitoren), wie Dabrafenib (150 mg zweimal täglich) und Trametinib (2 mg einmal täglich) zugelassen [29]. Dieser Ansatz geht auf die

Studie von Subbiah et al. zurück, in der die Verträglichkeit und eine Gesamtansprechrate (*overall response rate*, ORR) von 69 % (11 von 16, 95%-iges CI: 41-89 %) für diese Therapie bei Patienten mit mutiertem *BRAF V600E*-ATC nachgewiesen wurden (*BRAF*-Mutation mit Valin [v] anstelle von Glutaminsäure [e] an der Position 600) [29,75]. Bei *BRAF*- und *MEK*-negativen Tumoren werden *neurotrophic tyrosine receptor kinase* Genfusionen (*NTRK*-Genfusionen) als alternativer Angriffspunkt verwendet [57]. Bei Patienten ohne *BRAF*- und *MEK*-Mutationsnachweis und fortgeschrittenen initialen Befund mit *NTRK*-Genfusion besteht die Möglichkeit einer Systemtherapie mit Larotrectinib [57]. Wegen einer hohen Sicherheit und einer ORR von 75 % (95%-iges CI: 61-85 %) bei TC wurde im unabhängigen Review auch dieses Medikament von der FDA 2018 zugelassen [51,76]. Die *anaplastic lymphoma kinase (ALK)*-genfusionierten ATCs sind selten, weshalb ALK-Inhibitoren bisher hauptsächlich in klinischen Studien oder Fallberichten zum Einsatz kamen [35,77,78]. Außerdem gibt es Hinweise auf eine Prognoseverbesserung beim Einsatz von Immuncheckpoint-Inhibitoren bei der Behandlung von ATCs [79–81]. Bei einer initial erhöhten Tumormutationslast und *programmed cell death protein 1 ligand* (PD-L1) *tumor proportion scores* (TPS) können bei soliden Tumoren auch Inhibitoren von PD-L1 oder *programmed cell death protein 1* (PD-1) eingesetzten werden [82,83]. Obwohl die Datenlage zu dieser Therapie bisher eingeschränkt ist, wurden bereits 2018 die Sicherheit und eine vielversprechende Ansprechrate von 19.5 % des PD-1-Antikörpers Spartalizumab bei der Behandlung von mehrfach vorbehandelten ATCs beschrieben [29,84]. Außerdem wurde in einer Studie zu fortgeschrittenen ATCs mit Progression unter der Therapie mit Tyrosinkinaseinhibitoren Pembrolizumab hinzugefügt, wodurch eine *partial response rate* (PR-Rate) von 42 % und eine *stable disease* (SD) von 33 % erreicht werden konnten [81]. Bei einer Kombination von Lenvatinib und Pembrolizumab als Erstlinientherapie ergaben ergab sich eine *complete response* (CR) von 66% und eine SD von 16% [80]. Ähnlich wurde in einem Case Report gezeigt, dass eine neoadjuvante und *BRAF/MEK*-gerichtete Immuntherapie nach einer initialen Progression zusätzlich mit dem Checkpoint-Inhibitor Pembrolizumab kombiniert werden kann [85]. Dies führte zu einer PR und der anschließenden Möglichkeit einer vollständigen chirurgischen Resektion und einer adjuvanten Radiochemotherapie [85]. Bei dem Patienten soll diese Behandlung eine hohe Lebensqualität und eine CR innerhalb der 11-monatigen Follow-Up-Zeit ermöglicht haben [85]. Weitere Studien sind erforderlich, um „targeted therapies“ beim ATC zu etablieren. Aktuell wird dieses Thema in verschiedenen klinischen Studien (*national clinical trials*, NCTs) untersucht: NCT04171622, NCT04675710, NCT03122496, NCT01236547, NCT04238624, NCT03975231, NCT05119296, NCT03181100 [86–93].

Im kurativen Setting und dabei vor allem in den Stadien IVA und IVB wird die Kombination einer initialen Resektion und einer anschließenden simultanen Radiochemotherapie als eine multimodale oder trimodale Therapie eingesetzt [29,35,57]. Fan et al. konnten in einer Untersuchung von 104 ATC-Patienten zeigen, dass die multimodale Therapie in der multivariaten Analyse signifikant mit einem verbesserten progressionsfreien Überleben korrelierte (*hazard ratio* [HR] 0.060; p = 0.017) [70]. Dass dieser Ansatz zu einer Verbesserung des Gesamt- und progressionsfreien Überlebens führt, konnte auch von anderen Studien bestätigt werden [94–99].

Im metastasierten ATC-Stadium IVC bleiben die individuellen Prognosefaktoren des Patienten entscheidend für die weitere Therapieplanung [29,35,51]. Die NCCN-Leitlinien empfehlen eine aggressive Therapie mit einer Resektion und einer adjuvanten Radiotherapie (RT) und/oder Chemotherapie (ChT) oder eine palliative Therapie mit einem Fokus auf einer lokoregionären Kontrolle durch RT oder ChT, *best supportive care* und einer lokalen Kontrolle der Fernmetastasen [51]. In beiden Fällen kann eine Untersuchung von *BRAF/MEK*-Mutationen dabei helfen, die geeigneten Patienten für eine Immuntherapie zu identifizieren [29,51]. Bei der ATC-Behandlung ist

auch das Management der Atemwege sehr wichtig, wobei eine Tracheostomie eine der möglichen Optionen bildet [46,100,101]. Dennoch sollte dieser Eingriff multidisziplinär diskutiert werden [35,46]. Es ist anzunehmen, dass er mit einer deutlich verringerten Lebensqualität und aufgrund lokaler Komplikationen mit einem schlechteren Therapieergebnis verbunden ist, vor allem wenn er außerhalb von Notfallsituationen elektiv bzw. vor einer RT durchgeführt wird [46,100,102]. Dies kann auf das initial aggressivere Tumorwachstum, größere Tumormasse und die mit der Intervention verbundenen Komplikationen zurückgeführt werden [35,46,101]. Alternativ können neben den physikalischen Maßnahmen eine oft vorhandene Dyspnoe und Stridor effektiv durch eine kurzfristige Steroidtherapie behandelt werden [35].

2.4 Radiotherapie und Fraktionierungsschemata beim ATC

Die Strahlentherapie wird beim ATC sowohl im kurativen als auch im palliativen Setting angewendet [35]. In Abhängigkeit von der Zielsetzung ergeben sich unterschiedliche Fraktionierungsschemata und Bestrahlungsdosen, die bisher aber nicht verbindlich festgelegt wurden [103]. In einer der größten retrospektiven Studien von Glaser et al. mit insgesamt 3553 Patienten mit ATC konnte in der multivariaten Analyse eine deutliche Verbesserung des Gesamtüberlebens bei den Patienten nachgewiesen werden, die eine Gesamtdosis über 59.4 Gray (Gy) erhielten (HR_{Death} 0.41 [95%-iges CI 0.35-0.49], $p < .0005$). Ähnliche Dosis-Wirkungs-Zusammenhänge konnten auch in weiteren Studien für Dosen über 59 Gy, 50 Gy und 40 Gy festgestellt werden [49,104,63]. Konventionell werden im definitiven bzw. adjuvanten Setting normofraktioniert 1.8-2.2 Gy pro Fraktion mit einer Gesamtdosis von 70 bzw. 66 Gy eingesetzt [35]. Alternative Bestrahlungsschemata befinden sich jenseits der konventionellen Fraktionierung und werden deshalb als hypo- (≥ 2.2 Gy/Fraktion) oder hyperfraktionierte (< 1.8 Gy/Fraktion) RT bezeichnet [105]. Hinsichtlich der nationalen und internationalen Leitlinien gibt es beim ATC unterschiedliche Empfehlungen zur Fraktionierung [35,51,106]. Um das Verhältnis für die jeweilige Fraktionierung begründen zu können, ist es wichtig, den radiobiologischen Hintergrund der Fraktionierung zu erläutern. Die Überlebenswahrscheinlichkeit von Zellen im Gewebe nach einer Strahlenexposition wird im linearquadratischen Modell durch den folgenden Zusammenhang beschrieben [107]:

$$S = e^{-\alpha D - \beta D^2}$$

Dabei entspricht D der Expositionsdosis und α und β stehen für die zelluläre Radiosensitivität [107]. Das Verhältnis zwischen α und β entspricht der Dosis in Gy, bei der die Zellen im bestimmten Gewebe sowohl durch die lineare als auch durch quadratische Komponente der Gleichung gleichermaßen eliminiert werden [107]. Daran zeigt sich eine ausgeprägte Gewebespezifität, wobei spezifische Parameter für unterschiedliche Tumoren beschrieben wurden [108–110]. Die meisten Tumore weisen eine hohe Zellproliferationsrate auf und zeigen typischerweise α/β-Werte von über 10 Gy, weshalb sie mit einer konventionellen Fraktionierung am sichersten eliminiert werden können [107,108]. Allerdings wird bei radioresistenten Tumoren von einem kleineren α/β-Verhältnis ausgegangen, wie es für Melanome, Sarkome und das Prostatakarzinom beschrieben wurde [108,111]. Dabei kann die hypofraktionierte RT eingesetzt werden, um vergleichbare oder sogar bessere therapeutische Ergebnisse zu erzielen [112–115]. Das ATC gilt als radioresistent, und zwar u. a. wegen der pathophysiologischen Mutationen, die eine wichtige Rolle bei der Karzinogenese dieser Entität spielen [116–118]. Außerdem wurden optimierte hypofraktionierte RT-Schemata auch für andere und z. T. schnell wachsende Karzinome der Kopf-Hals-Region beschrieben [119]. Im Blick auf die kurze Lebenserwartung, eine Fokussierung auf den Erhalt der

Lebensqualität und die suffiziente lokale Kontrolle (*local control*, LC) bietet sich beim ATC eine Hypofraktionierung als eine geeignete Alternative für die Behandlung der Patienten an, bei der aber eine genauere Untersuchung erforderlich ist.

2.5 Der Hintergrund und ein Überblick zu den Publikationen

Die Veröffentlichungen beziehen sich auf die von mir retrospektiv erhobenen Daten der Patienten mit ATC im Stadium IVA bis IVC, die am LMU-Klinikum definitiv adjuvant oder palliativ behandelt wurden.

2.5.1 Publikation I

Das Überleben der ATC-Patienten bleibt eingeschränkt und bisher wurden keine genaueren therapeutischen Regimes festgelegt [103]. Wegen des kurzen Gesamtüberlebens und des aggressiven Wachstumsmusters des ATCs sind eine effiziente LC und eine Kontrolle der Symptome von besonderer Bedeutung für die allgemeine Lebensqualität der Patienten [35,120]. Hinsichtlich der pathophysiologisch auftretenden Mutationen und der klinischen Erfahrung gilt das ATC als relativ radioresistent [116–118]. Deshalb bildet die hypofraktionierte Bestrahlung u. a. nach dem linear-quadratischen Modell eine legitime therapeutische Option, weil dadurch innerhalb eines kürzeren Zeitraums ein vergleichbares oder sogar besseres Therapieansprechen erreicht werden kann [116–118]. Die Hypofraktionierung bei der Behandlung von ATC wurde bereits in einigen Studien untersucht [116,121–124]. Das Ziel der ersten Studie bestand darin, die Ergebnisse und die Toxizitäten bei der Behandlung von ATC mit dem hypofraktionierten Therapieschema in unserem tertiären Versorgungszentrum zu bewerten, ein systematisches Review mit einer gepoolten Datenanalyse zu erstellen und dabei Prognosefaktoren für das Gesamtüberleben (*overall survival*, OS) der Patienten zu identifizieren.

In der vorliegenden Publikation wurden die prognostischen Faktoren, Toxizität und Behandlungserfolge bei insgesamt 71 Patienten mit ATC untersucht. Dabei wurden die Daten aus unserem Zentrum (n = 11, welche den Einschlusskriterien entsprachen), sowie zusammengeführte externe Patientendaten aus unserem durchgeführten systematischen Review (n = 60), analysiert [121–123]. Die uni- und multivariate Analyse umfasste beide Kohorten und verglich das hypofraktionierte Regime mit konventioneller Fraktionierung mittels *propensity score matching* (PSM). In der unizentrischen Kohorte korrelierte dabei die multimodale Therapie ($p = 0.006$) und das männliche Geschlecht ($p = 0.04$) mit einem verbesserten Überleben. Schwerewiegende Nebenwirkungen der Grade 4 und 5 gemäß der *Common Terminology Criteria for Adverse Events* (CTCAE) Version 4 wurden nicht beobachtet. Bei der gepoolten Analyse erwies sich eine multimodale Behandlung bestehend aus einer tumorgerichteten Operation, ChT und RT univariat als signifikant für das verbesserte OS ($p < 0.001$). Des Weiteren zeigte sich, dass eine kumulative Strahlendosis ≥ 50 Gy, gemessen in einer Äquivalentdosis von 2-Gy-Fraktionen (*equivalent dose in 2-Gy fractions*, EQD2), in univariater Analyse signifikant mit dem verbesserten OS assoziiert war ($p = 0.014$). Bei der sukzessiven multivariaten Analyse zeigte sich nur die multimodale Therapie als ein unabhängiger Prädiktor für ein besseres OS ($p = 0.003$, HR: 0.636, 95%-iges CI: 0.469–0.861). Patienten, die mit einer normofraktionierten RT behandelt wurden, wurden im Verhältnis 1:2 mit Patienten gematcht, die mit einer hypofraktionierten RT behandelt wurden. Jedem Patienten, der mit einer normofraktionierten RT behandelt wurde, wurden zwei entsprechende Patienten mit demselben *performance score* gemäß *Eastern Cooperative Oncology Group* (ECOG)

und Geschlecht zugeordnet. Nach dem PSM ergab sich bei dem Fraktionierungsverfahren bei der univariaten Analyse keine Signifikanz (p = 0.372). Deshalb scheint die hypofraktionierte Strahlentherapie im Vergleich mit der normofraktionierten RT hinsichtlich des OS nicht unterlegen zu sein, sodass sie ein integraler Bestandteil der multimodalen Behandlung werden könnte, was in weiteren Studien untersucht werden sollte.

2.5.2 Publikation II

Patienten im höheren Alter kommt eine besondere Stellung bei der onkologischen Behandlung zu, weil sie oft einen multimorbiden und reduzierten Allgemeinzustand (z.B. KPS) aufweisen [125–129]. Diese Patientenkohorte (≥ 65 Jahre) ist allerdings beim ATC besonders stark repräsentiert [6, 43, 46, 66, 114]. Das Gesamtüberleben und die Prognose sind unter diesen Bedingungen stark eingeschränkt und das höhere Alter wurde in mehreren Studien als negativer prognostischer Faktor für das OS beim ATC eingestuft [49,64,131–133]. Unsere Hypothese besagte, dass eine suffiziente LC bei diesem eine Therapie relativ schlecht tolerierenden Kollektiv deshalb besonders wichtig wäre. Die hypofraktionierte Therapie könnte eine geeignete Behandlungsalternative für ältere Patienten werden, zunächst sollten aber individuelle prognostische Faktoren und mögliche RT-bedingte Toxizitäten für dieses Kollektiv genauer untersucht werden. Die zweite Studie wurde daher konzipiert, um das Alter als einen prognostischen Faktor bei älteren Patienten mit ATC zu evaluieren. Dabei wurden konsekutiv alle ATC-Patienten, die bei der Erstdiagnose ≥ 65 Jahre alt waren, hinsichtlich der Ergebnisse und einer behandlungsbedingten Toxizität untersucht. Außerdem wurden in diesem Kollektiv individualisierte prognostische Faktoren für das OS und das progressionsfreie Überleben (*progression-free survival*, PFS) erfasst.

In der vorliegenden Publikation sollten die Ergebnisse und die therapiebedingte Toxizität bei älteren Patienten (≥ 65 Jahren) mit ATC, die eine (Chemo-)RT erhielten, uni- und multivariat bewertet und prognostische Faktoren für das OS ermittelt werden. Dabei wurden die Daten aus unserem Zentrum (*n* = 26) evaluiert, welche den Einschlusskriterien entsprachen. Eine separate Analyse beinhaltete zusammengeführte externe Patientendaten aus unserem durchgeführten systematischen Review (*n* = 186) [61,96,121–123,134–136]. Bei der unizentrischen Kohorte ergab sich bei der univariaten Analyse eine Assoziation von *Karnofsky Performance Score* (KPS) > 70 % (p <0.001), N-Status (p = 0.028), M-Status (p = 0.001), UICC-Stadium IVA (p = 0.004), multimodaler Behandlung (p < 0.001) und einer EQD2 > 49 Gy (p < 0.001) mit einem verbesserten OS. Ähnliche Ergebnisse wurden univariat auch für das progressionsfreie Überleben erzielt: KPS > 70 % (p = 0.025), N-Status (p < 0.001), M-Status (p = 0.030), Tumorresektion (p < 0.001), multimodale Behandlung (p < 0.001) und ein EQD2 > 49 Gy (p = 0.006). In ähnlicher Weise wurde auch die gepoolte Kohorte univariat analysiert, wobei eine chirurgische Resektion (p < 0.001), RT (p < 0.001), eine sequenzielle oder konkurrente ChT (p < 0.001) und eine multimodale Therapie (p < 0.001) als wichtige prognostische Faktoren für das verbesserte OS identifiziert werden konnten. Bei der multivariaten Analyse zeigte sich nur die RT (p < 0.001, HR = 0.383, 95%-iges CI = 0.253-0.579) als ein unabhängiger prognostischer Faktor für das verbesserte OS. Danach wurde ein PSM durchgeführt. Dabei wurden die Patienten im Alter von ≤ 64 Jahren im Verhältnis 1:1 mit Patienten im Alter von ≥ 65 Jahren gematcht. Jedem Patienten im Alter von ≤ 64 Jahren wurde ein entsprechender Patient im Alter von ≥ 65 Jahren mit demselben UICC-Stadium (IV A/B vs. IVC) zugeordnet, wobei auch die Art der Behandlung berücksichtigt wurde, einschließlich Operation und ChT. In diesem Zusammenhang waren bei der multivariaten Analyse eine Tumorresektion (p < 0.001, HR = 0.294, 95%-iges CI = 0.192-0.45), eine RT (p < 0.001, HR = 0.042, 95%-iges CI = 0.018-0.098) und ein jüngeres Patientenalter (p = 0.008, HR = 1.721, 95%-iges CI =

1.151-2.573) signifikant mit einem verbesserten OS verbunden. Mit dieser Studie konnte gezeigt werden, dass das jüngere Patientenalter ein unabhängiger prognostischer Faktor für das verbesserte OS bei der Behandlung des ATC ist. Eine multimodale Behandlung des ATC mit einer Operation und Radiochemotherapie scheint bei tolerierbarer Toxizität bei Patienten im höheren Alter von über 64 Jahren mit vielversprechenden Ergebnissen verbunden zu sein.

2.5.3 Publikation III

Bei der Diagnosestellung weisen viele ATC-Patienten bereits Fernmetastasen auf [4,40–42]. Das Vorliegen der Fernmetastasen ist ein negativer prognostischer Faktor, der mit einem kürzeren Überleben verbunden ist [40,45,48–50,70]. Die oft vorhandenen lokalen Symptome, wie Dyspnoe, Dysphagie und Heiserkeit, verdeutlichen die Relevanz einer effizienten LC [43–45]. Die Datenlage für die Verwendung der RT im Stadium IVC ist nach wie vor eingeschränkt [40,63,137]. Eine suffiziente RT des Primärtumors scheint auch im Stadium IVC mit einer verbesserten Überlebensrate und einer besseren lokalen Kontrolle verbunden zu sein [63,70]. Eine hypofraktionierte RT stellt deshalb für diese Patienten eine wichtige Behandlungsalternative dar, die hypothetisch mit vergleichbaren Ergebnissen bei einem geringeren Zeitaufwand verbunden sein kann. Die neuen immunologischen Verfahren können zu deutlichen Verbesserungen beim Therapieansprechen führen, weshalb eine Untersuchung der RT-Wirkung in einem fortgeschrittenen Stadium für die Perspektive einer Kombination mit neuen Systemtherapien als unentbehrlich erscheint [75,76,81,84]. Die Identifikation besonderer Patientengruppen ist dabei für eine individualisierte Therapieplanung von besonderer Bedeutung. Deshalb ging es bei der dritten Publikation vor allem um eine Evaluation der prognostischen Faktoren und der Therapieergebnisse der ATC-Patienten im Stadium IVC, die am Primärtumor bestrahlt wurden.

In der vorliegenden Studie wurden prognostische Faktoren und Therapieergebnisse bei bestrahlten Patienten mit metastasiertem ATC (n = 20) aus unserem Zentrum analysiert. Bei der univariaten Analyse konnten eine Tumorresektion (p = 0.005), eine sequenzielle oder konkurrente ChT (p = 0.018) und eine Erhöhung der Bestrahlungsdosis (> 39 Gy, p = 0.038) als prognoseverbessernde Faktoren für das OS identifiziert werden. Außerdem ergab sich bei einem KPS > 70 % ein Trend zu einer längeren Überlebenszeit (p = 0.062). Bei der multivariaten Analyse konnte bei keinem Faktor Signifikanz für das OS erzielt werden. Allerdings waren eine kleine Anzahl von Metastaseherden (1 vs. 2-4 Herde, p = 0.043), eine Operation (p = 0.024) und eine ChT (p = 0.039) mit einem verbesserten PFS verbunden. Insgesamt wurde keine Toxizität der Grade 4-5 gemäß CTCAE beobachtet. Bei einem metastasierten ATC ermöglicht die Strahlentherapie des Primärtumors eine dauerhafte LC. Eine Kombination aus gleichzeitiger oder sequenzieller Chemotherapie und einer Erhöhung der Strahlendosis wurde bei Patienten mit metastasierter Erkrankung mit längeren Überlebensraten in Verbindung gebracht und sollte deshalb in ausgewählten Fällen in Betracht gezogen werden.

2.5.4 Publikation IV

Wie bereits beschrieben wurde, sind bei der Erstdiagnose des ATC oft bereits Fernmetastasen vorhanden, was mit einer besonders schlechten Prognose verbunden ist [3,4]. Die Fragen hinsichtlich der Notwendigkeit und des optimalen chirurgischen Eingriffs bleiben in diesem Stadium offen [29,57]. Zu den Optionen für eine chirurgische Behandlung von ATC gehören nach den Leitlinien der ATA die totale Thyreoidektomie, die subtotale Thyreoidektomie und die Hemithyreoidektomie [35]. Aktuelle Leitlinien empfehlen eine totale Thyreoidektomie auch im Stadium IVC, wenn eine R0/R1-Resektion erreicht werden kann, während eine Debulking-Operation generell nicht empfohlen wird [29,35,51]. Das Ausmaß des Eingriffs wird maßgeblich durch die initiale Tumorausbreitung bestimmt [35,138]. Durch die oft vorhandenen Infiltrationen der benachbarten Strukturen besteht die Option einer ultra-radikalen Resektion einschließlich Laryngektomie, einer Resektion der infrahyoiden Muskulatur, der Trachea oder des Ösophagus [138]. Sugitani et al. konnten einen Überlebensvorteil durch eine ultra-radikale Operation bei Patienten mit einem ATC IVB feststellen [138]. Allerdings konnte dies in weiteren Studien nicht bestätigt werden, da die Morbidität und die operativen Risiken oft den potenziellen Nutzen radikaler Resektionen überwogen [59]. Eine möglichst vollständige Reduktion der Tumorlast bleibt jedoch die entscheidende Voraussetzung für eine effiziente LC und ein besseres Ansprechen auf die RT [45,70]. Deshalb ist es wichtig, die vorhandenen chirurgischen Optionen bei der Behandlung von ATC IVC hinsichtlich der allgemeinen und krankheits-spezifischen Überlebensraten miteinander zu vergleichen. Die vorliegende im *Journal of Cancer Research and Clinical Oncology* publizierte Studie wurde daher mit dem Ziel einer Evaluation der Thyreoidektomie-Verfahren hinsichtlich des OS und des krankheitsspezifischen Überlebens (*disease-specific survival*, DSS) konzipiert und durchgeführt.

In der vorliegenden Arbeit wurden zwei große Patientenkollektive analysiert. Dabei wurden zum einen die Operation des Primärtumors und ihre Kombination mit systemischen und lokalen Therapien beim metastasierten ATC bei insgesamt 123 Patienten evaluiert. Die erste Kohorte setzte sich zusammen aus einem kombinierten Datensatz von unserem Zentrum (n = 20) und externen Patientendaten, die aus unserem durchgeführten systematischen Literaturreview stammen (n = 103) [61,73,95,96,121–123,135,136,139]. Die zweite Kohorte wurde aus dem *Surveillance, Epidemiology, and End Results Register* (SEER) akquiriert (n = 617). Die gepoolte Kohortenstudie zeigte, dass eine Operation ($p < 0{,}001$), eine suffiziente RT ≥ 30 Gy ($p < 0.001$), eine Administration von ChT ($p < 0.001$) und eine multimodale Behandlung ($p = 0.014$) univariat zu einem verbesserten Gesamtüberleben führen. Bei der multivariaten Analyse waren eine Operation (HR = 1.997, 95%-iges CI = 1.162-3.433, $p = 0.012$) und eine suffiziente RT ≥ 30 Gy (HR = 1.877, 95%-iges CI=1.232-2.843, $p = 0.012$) unabhängige Prädiktoren für ein verbessertes Überleben. Bei den oben genannten Operationen wurde nicht weiter nach dem Operationstyp differenziert, daher handelte es sich um eine beliebige tumorgerichtete Operation. Bei den analysierten Operationsverfahren wurden die totale Thyreoidektomie in 28.2 % der Fälle, die subtotale Thyreoidektomie, die Hemithyreoidektomie und die Debulking-Operation jeweils in 10.3 %, 5.1 % bzw. 12.8 % der Fälle durchgeführt. In der anschließenden univariaten Analyse zeigte die totale Thyroidektomie eine Tendenz zu einem verbesserten OS im Vergleich zu anderen Operationstypen, mit Überlebensraten von 45 bzw. 30 % nach 9 Monaten ($p = 0.058$). In der SEER-basierten Studie mit Patienten, die sich einer tumorbezogenen Behandlung unterschiedlicher Art unterzogen (n = 445), korrelierten die totale Thyreoidektomie ($p = 0.031$), die Verabreichung einer ChT ($p = 0.007$), eine RT ($p < 0.001$), eine Kombination von Operation und RT mit oder ohne ChT (p

< 0.001) und die multimodale Behandlung (p < 0.001) univariat mit einem DSS. Bei der multivariaten Analyse war die Debulking-Operation ein unabhängiger Prädiktor für ein schlechteres Ergebnis (p = 0.010, HR = 0.535, 95%-iges CI: 0.332-0.862), während die Verabreichung einer RT mit einem längeren DSS korrelierte (HR = 2.316, 95%-iges CI: 1.362-3.939, p = 0.002). Bei den operierten Sub-Kohorten aus dem SEER-Register korrelierten die totale Thyreoidektomie (p = 0.031), die Verabreichung einer ChT (p = 0.007), die RT (p < 0.001), eine Kombination aus Operation und RT mit oder ohne ChT (p < 0.001) und die multimodale Behandlung (p < 0.001) mit einem verbesserten DSS univariat. Außerdem ergab sich bei der Debulking-Operation eine reziproke Proportionalität mit dem DSS (p < 0.001). Bei der multivariaten Analyse war die Debulking-Operation ein unabhängiger Prädiktor für ein schlechteres DSS (HR = 0.535, 95%-iges CI: 0.332-0.862, p = 0.010), während die RT-Verabreichung mit einem längeren DSS korrelierte (HR = 2.316, 95%-iges CI: 1.362-3.939, p = 0.002). Insgesamt erwies sich in der vorliegenden Studie die Operation des Primärtumors als Thyreoidektomie in jeder Form, aber nicht als Debulking, als ein wichtiger Faktor für eine Verbesserung des Gesamt- und krankheitsspezifischen Überlebens bei den ATC-Patienten mit Fernmetastasen aus der SEER-Datenbank.

3. Zusammenfassung

Das anaplastische Schilddrüsenkarzinom (ATC) ist eine seltene, aber äußerst aggressive Erkrankung [1-7]. Die meisten Patienten sterben an dieser Erkrankung oder ihren Folgen innerhalb der ersten 6-12 Monate nach der Diagnose [6-7]. Bei den UICC-Stadien IVA und IVB ist die Strahlentherapie ein fester Bestandteil der Behandlung [29,35,57,137]. Die Entscheidung für eine RT im Stadium IVC hängt allerdings vor allem vom Allgemeinzustand des Patienten, vom Behandler und vom Mutationsstatus ab, weshalb keine allgemeingültige Behandlungsempfehlung möglich ist.

Die hypofraktionierte RT ist eine mögliche Behandlungsoption für ATC-Patienten, und zwar insbesondere im metastatischen Stadium, da eine solche lokale Therapie vergleichsweise kurz ist und die systemische Therapie daher nicht lange aufgeschoben werden muss. Darüber hinaus ergab sich präklinisch, dass mit hypofraktionierten Konzepten zumindest vergleichbare Ergebnisse erzielt werden können [116]. Gegenstand der vorliegenden kumulativen Arbeit war eine Untersuchung hypofraktionierter Therapiekonzepte für die Behandlung von ATC, wobei besondere Zielgruppen wie ältere Patienten (≥ 65 Jahre), das metastasierte Stadium und die Integration anderer Therapiemodalitäten im Vordergrund standen.

In der systematischen Übersichtsarbeit und gepoolten Analyse der hypofraktionierten Strahlentherapie bei anaplastischem Schilddrüsenkarzinom wurden prognostische Faktoren, die Toxizität und der Behandlungserfolg bei 71 Patienten mit ATC untersucht und die hypofraktionierten Therapieschemata wurden mit der konventionellen Fraktionierung durch PSM verglichen. Dabei konnte nachgewiesen werden, dass dieses Fraktionierungsverfahren im Vergleich mit der konventionellen Fraktionierung hinsichtlich der Ergebnisse und der Toxizität nicht unterlegen war. Darüber hinaus konnten multimodale Behandlungsansätze und eine Dosiseskalation von EQD2 > 50 Gy als signifikante prognostische Faktoren für das verbesserte Überleben identifiziert werden.

Die zweite Studie beschäftigte sich vor allem mit einer Bewertung der behandlungsbedingten Toxizität bei älteren Patienten (65 Jahre und älter), die sich einer multimodalen Behandlung von anaplastischem Schilddrüsenkrebs unterzogen. Die Studie bezog sich sowohl auf die Patientenkohorte von 26 Patienten aus unserer Institution als auch auf eine gepoolte Kohorte von 186 Patienten. Dabei wurden prognostische Faktoren ermittelt, die nur für diese Patientengruppe gelten, und die Prävalenz der häufigsten Grad 3 Toxizitäten wurde anhand der CTCAE bewertet. Die Ergebnisse deuten darauf hin, dass für diese spezielle Patientenkohorte ein multimodaler Therapieansatz, bestehend aus einer tumorgerichteten Operation, systemischer Therapie und adjuvanter Strahlentherapie, hinsichtlich der Verträglichkeit in Betracht gezogen werden könnte.

In der dritten Studie wurden prognostische Faktoren und Behandlungsergebnisse in einer Kohorte von n = 20 Patienten mit metastasiertem ATC untersucht, die in unserem Zentrum behandelt wurden und dennoch eine Bestrahlung des Primärtumors erhielten. Bei Patienten mit metastasiertem ATC konnte durch die Bestrahlung eine günstige LC erreicht werden. Darüber hinaus konnte nachgewiesen werden, dass eine Intensivierung der Behandlung durch gleichzeitige oder sequentielle Chemotherapie und Eskalation der Strahlendosis auch bei fortschreitender Erkrankung mit einem verbesserten Überleben korreliert.

Bei der letzten Studie geht es um eine SEER-basierte Bewertung der chirurgischen Behandlung des Primärtumors bei metastasiertem ATC. Dabei sollte die Integration von chirurgischen oder anderen Behandlungsoptionen und prognostischen Faktoren bei metastasiertem ATC anhand von zwei großen Kohorten von 123 bzw. 617 Patienten bewertet werden. Ein wichtiges Ergebnis

besteht dabei u. a. darin, dass die R0/R1 Operation, im Gegensatz zum Debulking, sowie die Bestrahlung ≥ 30 Gy mit einem signifikant verlängertem Gesamtüberleben assoziiert sind. Eine Debulking Operation war ein unabhängiger Faktor für ein schlechteres, die Bestrahlung für ein verbessertes krankheitsspezifisches Überleben.

Zusammenfassend lässt sich feststellen, dass hypofraktionierte Therapiekonzepte insbesondere beim metastasierten Stadium IVC und einem günstigen Nebenwirkungsprofil eine angemessene Therapieoption darstellen können, die u. a. auch bei der multimodalen Behandlung und bei älteren Patienten eingesetzt werden kann (≥ 65 Jahre).

4. Abstract

Anaplastic thyroid carcinoma (ATC) is a rare yet extremely aggressive condition [1-7]. The majority of patients succumb to the disease within the first 6 to 12 months following diagnosis [6-7]. Radiotherapy is an integral part of therapy in Union Internationale Contre le Cancer (UICC) stages IVA and IVB [29,35,57,137]. However, the decision to RT in stage IVC largely depends on the patient's general condition, treatment provider, and mutation status, so no universal treatment recommendation can be established.

Hypofractionated RT is a possible treatment option for ATC patients, especially in the metastatic stage, since such local therapy is comparatively short and systemic therapy will not be postponed for a long time. Furthermore, it has been shown preclinically that hypofractionated concepts can achieve at least comparable results [116]. This work aims to investigate hypofractionated therapy concepts in the treatment of ATC with a focus on particular target groups like elderly patients (≥65 years), metastatic stage, and the integration of other therapy modalities.

In the systematic review and pooled analysis of hypofractionated radiotherapy for anaplastic thyroid cancer we analyzed prognostic factors, toxicity, and treatment success of 71 patients with ATC and compared the hypofractionated regimens with conventional fractionation by PSM. This fractionation regimen was shown to be non-inferior to conventional fractionation concerning outcome and toxicity. In addition, multimodality treatment approaches and dose escalation from EQD2 > 50Gy were identified as significant prognostic factors for a better overall survival.

The second study was focused on evaluating treatment-related toxicity in elderly patients (aged 65 and above) who underwent multimodal treatment for anaplastic thyroid cancer. The study involved both the patient cohort of 26 patients from our institution and a pooled cohort of 186 patients. Prognostic factors unique to this patient group were identified, and the prevalence of the most common grade 3 toxicities according to the CTCAE was evaluated. The results suggest that for this specific patient cohort, a multimodal treatment approach, consisting of tumor-directed surgery, systemic therapy, and adjuvant radiotherapy, could be considered for its tolerability.

The third study examined prognostic factors and treatment results in a cohort of n = 20 patients who developed metastatic ATC treated at our center and yet received irradiation to the primary tumor site. Patients with metastatic ATC had a beneficial local control when irradiated. Furthermore, it has been demonstrated that intensifying treatment through simultaneous or sequential chemotherapy and escalation of the radiation dose is also correlated with improved survival in cases of progressive disease.

The last study is a SEER-based evaluation of surgical treatment of the primary tumor in metastatic ATC. Hence, it aims to evaluate the integration of surgery or different surgical treatment options and prognostic factors in metastatic ATC using two large cohorts of 123 and 617 patients, respectively. An important finding is that R0/R1 surgery, in contrast to debulking, as well as radiation therapy ≥ 30 Gy, are associated with significantly prolonged overall survival. A debulking surgery was an independent predictor for worse, while radiation therapy was associated with improved disease-specific survival.

In summary, hypofractionated therapy concepts are shown to be an appropriate treatment option, especially in metastatic ATC stage IVC with a favorable side effect profile, within the multimodality treatment framework, and in elderly patients (≥ 65 years).

5. Paper I

cancers

MDPI

Article

Hypofractionated Radiotherapy for Anaplastic Thyroid Cancer: Systematic Review and Pooled Analysis

Dmytro Oliinyk [1], Teresa Augustin [1], Viktoria Florentine Koehler [2], Josefine Rauch [1], Claus Belka [1,3], Christine Spitzweg [2,3] and Lukas Käsmann [1,3,*]

[1] Department of Radiotherapy and Radiation Oncology, University Hospital, LMU Munich, 81377 Munich, Germany; Dmytro.Oliinyk@med.uni-muenchen.de (D.O.); Teresa.Augustin@med.uni-muenchen.de (T.A.); Josefine.Rauch@med.uni-muenchen.de (J.R.); Claus.Belka@med.uni-muenchen.de (C.B.)

[2] Department of Internal Medicine IV, University Hospital, LMU Munich, 81377 Munich, Germany; viktoria.koehler@med.uni-muenchen.de (V.F.K.); Christine.Spitzweg@med.uni-muenchen.de (C.S.)

[3] German Cancer Consortium (DKTK), Partner Site Munich, 80336 Munich, Germany

* Correspondence: Lukas.Kaesmann@med.uni-muenchen.de; Tel.: +49-89440074511; Fax: +49-89440076770

Received: 17 July 2020; Accepted: 1 September 2020; Published: 3 September 2020

check for updates

Simple Summary: Anaplastic thyroid carcinoma is an aggressive cancer subtype with a dismal prognosis. Multimodal treatment approaches consisting of surgical resection, radiation therapy (RT) and chemotherapy have resulted in longer overall survival and promising outcomes. Hypofractionated RT is an alternative to conventional RT regimens. In this study, we aim to evaluate the outcome of hypofractionated regimens, perform a systematic review concerning hypofractionated RT and pooled analysis of this treatment modality. Hypofractionated RT appears to be non-inferior compared to conventional RT concerning OS after propensity score matching. In addition, radiation dose escalation correlated with a longer OS. In conclusion, hypofractionated RT is effective with manageable toxicity and could be an integral part in multimodal treatment.

Abstract: Anaplastic thyroid carcinoma (ATC) is associated with a poor prognosis due to aggressive tumor growth and high treatment resistance. Hypofractionated treatment concepts may be more effective and less time consuming compared to normofractionated radiotherapy (RT). In this retrospective study, we aim to evaluate the outcome of hypofractionated regimens and perform a systematic review concerning hypofractionated RT and pooled analysis of this treatment modality. A systematic review using the MEDLINE/Pubmed and Cochrane databases was performed. Data from all eligible studies were extracted, and a pooled analysis of literature and our cohort (n = 60) was carried out to examine patient characteristics, toxicity, and outcomes of patients with ATC. As a result, median overall survival (OS) of the single center cohort was four (range 1–12) months. Survival rates at one, three, and six months were 82%, 55%, and 36%, respectively. In univariate analyses, multimodal treatment (p = 0.006) and gender (p = 0.04) were correlated with an improved OS. Six studies with a total number of 152 patients undergoing hypofractionated RT treatment were analyzed. The pooled analysis included four patient cohorts with 60 patients and showed median OS of 5.3 (range: 1–24) months. Multimodal treatment (p < 0.001) and a cumulative radiation dose ≥50 Gy in equivalent dose in 2 Gy fractions (EQD2) (p = 0.014) correlated with an improved OS. On multivariate analysis, multimodal treatment (p = 0.003, hazard ratio (HR): 0.636, 95% confidence interval (CI): 0.469–0.861) was an independent predictor for longer OS. After propensity score matching (PSM), hypofractionated RT appears to be non-inferior compared to normofractionated RT concerning OS. In conclusion, hypofractionated RT is effective with manageable toxicity. A dose escalation with ≥50 Gy (EQD2) correlated with a longer OS. Hypofractionated RT could be an integral part in multimodal treatment with a promising outcome.

Keywords: ATC; anaplastic thyroid cancer; hypofractionated; irradiation; survival

1. Introduction

Anaplastic thyroid carcinoma (ATC) remains one of the rarest and most aggressive neoplasms of the thyroid gland, enumerating a relatively stable incidence of approximately 3.4% in Europe [1]. ATC confers a dismal prognosis due to rapid progression with a median overall survival (OS) of 3–6 months [2]. Current treatment modalities incorporate multimodality approaches including surgery, radiotherapy (RT), and chemotherapy, as well as novel systemic treatment approaches with increasing research on targeted therapies including druggable BRAF V600E or RAS mutations, RET, ALK or NTRK fusions, and PD-L1 overexpression [3,4]. Depending on resectability and stage of disease, surgery with adjuvant chemoradiotherapy or definitive RT with concurrent chemotherapy (ChT) (usually with doxorubicin or platinum-based agent) can be considered standard of care [5,6]. Quality of life (QoL) and locoregional control represent primary treatment goals and need to be taken into account for decision making. Patients' overall prognosis should be considered when tailoring the treatment regimen. With the aim of a personalized treatment approach, patients with a limited prognosis should preferably receive a short palliative regimen consuming as little of the patients' remaining lifespan as possible.

To date, several established fractionation regimens can be administered in patients with ATC. Conventional irradiation once daily with 2 Gy per fraction up to 70 Gy of total dose was used for ATC treatment as an established standard option according to National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines in Oncology [5] and American Thyroid Association Guidelines [7]. Historically, altered fractionation techniques, e.g., hyperfractionated RT, have been introduced but failed to achieve less toxicity or improved outcome [6,8–10]. Delivery of higher radiation doses per fraction over a shorter period of time in form of hypofractionated RT could theoretically have advantages in terms of quality of life (QoL) and achieving local control (LC). In the preclinical study of Oweida et al. [11], hypofractionated RT demonstrated enhanced local tumor control compared to normofractionated RT in a mouse model. In addition, several clinical studies found promising results concerning hypofractionated RT in the treatment of ATC [12–14]. The aim of the present study is to evaluate the outcome and toxicity of hypofractionated regimens in the treatment of ATC at our tertiary care center and to perform a systematic review of literature with a pooled data analysis.

2. Results

2.1. Single Center Evaluation

2.1.1. Treatment

A total of 17 ATC patients treated with hypofractionated RT at out center were identified. We excluded all patients treated in palliative intention and with a cumulative radiation dose ≤30 Gy. The remaining patients (n = 11) were included in the analysis. Total thyroidectomy was performed in three patients (27%), respectively, before irradiation. ChT was administered in six patients (55%), four patients (67% of ChT group) received ChT (carboplatin AUC 2 with Paclitaxel 50mg/m^2 or doxorubicin (10 mg/m^2) weekly) in combination with irradiation, while two patients (33% of ChT group) received ChT in a neoadjuvant concept with doxorubicin or carboplatin/paclitaxel before irradiation. Irradiation was administered using three-dimensional conformal RT (3D-CRT) technique in eight patents (73%), and three patients (27%) were treated using intensity modulated radiation therapy (IMRT). All patients were treated with single dose of 2.50 Gy (18%) or 3.00 Gy (82%). The cumulative radiation dose was calculated in equivalent dose in 2 Gy fractions (EQD2). The median EQD2 of our cohort was 49 (range 32–55) Gy (Table 1).

Table 1. Patient and treatment characteristics of single center cohort.

Parameter	*n*
Age, years	
<73	5 (46%)
≥73	6 (55%)
Gender	
Male	4 (36%)
Female	7 (64%)
ECOG-PS	
0	2 (18%)
1	7 (64%)
2	2 (18%)
T stage	
3	1 (9%)
4	10 (91%)
N stage	
0	1 (9%)
0	10 (91%)
M stage	
0	3 (27%)
1	8 (73%)
UICC stage	
IVB	3 (27%)
IVC	8 (73%)
Surgery	
No	8 (73%)
Yes	3 (27%)
Concurrent chemotherapy	
No	4 (36%)
Yes	7 (64%)
Treatment	
RT/CRT	8 (73%)
S+CRT	3 (27%)
EQD2 level	
< 45 Gy	5 (46%)
≥ 45 Gy	6 (55%)
RT technique	
3D-CRT	8 (73%)
IMRT	3 (27%)

ECOG-PS = Eastern Cooperative Oncology Group Performance Score, UICC = Union internationale contre la cancer, IVB/IVC staging according to 8th edition of UICC, RT = radiation therapy, CRT = concomitant chemoradiotherapy, S+CRT = chemoradiotherapy following surgical resection.

2.1.2. Outcome

Median OS of the single center cohort was 4 (range 1–12, 95% confidence interval (CI): 0.763–7.237) months. Survival at one, three, and six months was 82%, 55%, and 36%, respectively (Table 2, Figure 1A). No local progression was observed during RT or within follow up. In univariate analyses, multimodal treatment ($p = 0.006$) and gender ($p = 0.04$) correlated with an improved OS (Table 2, Figure 1B,C), respectively. On multivariate analysis for OS no factor achieved significance. Age ($p = 0.106$), Eastern Cooperative Oncology Group (ECOG) performance status ($p = 0.326$), and RT technique ($p = 0.701$) were not associated with OS.

Table 2. Uni- and multivariate analysis of overall survival (OS) in the single center cohort.

Parameter	At 3 Months	At 6 Months	At 9 Months	*p*-Value (Univariate Analysis)	*p*-Value (Multivariate Analysis)
Age, years					
<73	60%	40%	40%	0.106	
≥73	50%	17%	0%		
Gender					
Male	71%	57%	43%	**0.04**	0.349
Female	25%	0%	0%		
ECOG-PS					
0	100%	50%	50%		
1	57%	43%	29%	0.326	
2	0%	0%	0%		
M stage					
0	100%	67%	67%	0.179	
1	38%	25%	13%		
Treatment					
RT/CRT	38%	13%	0%	**0.006**	0.941
S+CRT	100%	100%	100%		
Concurrent chemotherapy					
No	57	29	14	0.327	
Yes	50	50	50		
EQD2 level					
<45 Gy	50%	33%	17%	0.241	
≥45 Gy	60%	40%	40%		
RT technique					
3D-CRT	50%	38%	38%	0.701	
IMRT	67%	33%	0%		

ECOG-PS = Eastern Cooperative Oncology Group Performance Score, UICC = Union internationale contre la cancer, IVA/IVB/IVC staging according to 8th edition of UICC, RT = radiation therapy, CRT = concurrent chemoradiotherapy, S+CRT = chemoradiotherapy following surgical resection, EQD2 = equivalent dose in 2Gy per fraction.

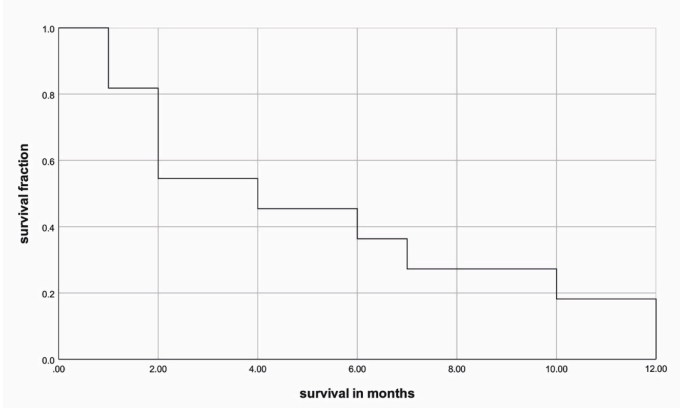
2.1.3. Treatment-Related Toxicity

Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4. The most frequent side effects of local radiation were dysphagia, dysphonia, dermatitis, and mucositis. Grade 3 acute toxicities of dysphagia, dysphonia, dermatitis, and mucositis were observed in 18%, 18%, 9%, and 9% of patients, respectively. Therapy-related toxicity grade 4/5 was not observed.

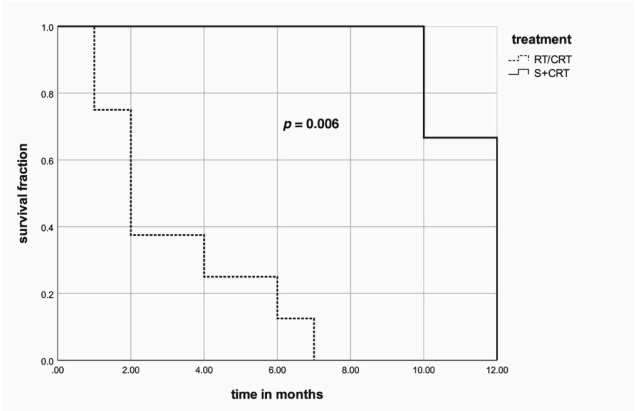
2.2. Systematic Review

In total, 267 studies were yielded by an initial literature search (MEDLINE/PubMed). Evaluation of the Cochrane database did not provide any eligible data. In total, 261 publications were manually excluded after abstract and full-text screening. Fifty-six of the excluded papers were reviews and hence inspected for relevant citations. All of the cited studies on hypofractionated RT were excluded due to the publication dates not meeting inclusion criteria. After abstract screening, 219 studies were excluded for reasons shown in Figure 2. A total of 48 publications was selected for full-text analysis. Six publications met inclusion criteria and were included in the systematic review (Figure 2; [12–17]). Included publications involved patient cohorts with heterogeneous stage distribution ranging from 26 to 62 patients [12–17]. Hypofractionated RT was administered to a total of 152 patients with at least 43% of all patients diagnosed in UICC stage IVC. Characteristics of patients, treatment modalities, symptoms, outcome, and toxicities that were reported in the included studies are shown in Tables 3–6.

A.



B.



C.

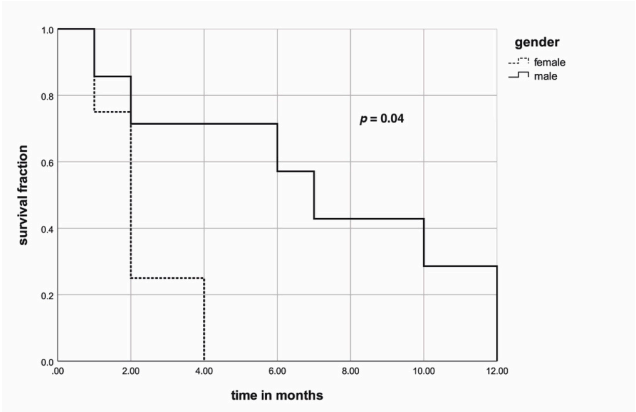


Figure 1. (**A**) Kaplan–Meier curve concerning overall survival of the single center cohort. (**B**) Kaplan–Meier curves concerning treatment mode for overall survival in the single center cohort. The *p*-value was calculated with the log-rank test. (**C**) Kaplan–Meier curves concerning gender for overall survival in the single center cohort. The *p*-value was calculated with the log-rank test.

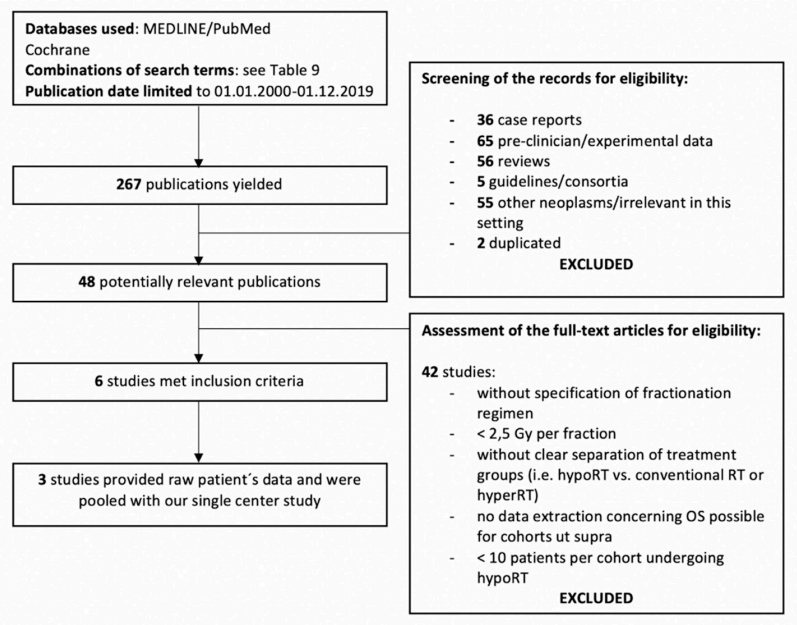


Figure 2. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for systematic review of literature with results summary.

Four studies [14–17] reported patient symptoms at initial diagnosis, but only Wang et al. [16] specified the symptoms of the cohort administered hypofractionated RT. Apart from the most common symptom of neck mass (73–88%), several impairments have been reported, including dysphagia (17–54%), dysphonia (31–50%), dyspnea (20–33%), and other [12,16]. Surgery and ChT was reported in 22–82% and 14–88% of hypofractionated RT treated patients, respectively. The median prescribed total dose was ≤54 Gy with the median dose per fraction ranging from 3 Gy to 5 Gy. Median OS was 3–9.3 months. Two authors reported a relatively long median OS of 9.3 and 6 months, respectively [12,14]. Survival rates at three, six, and 12 months were reported or calculated according to data of four authors [12,13,16,17]. Remarkably, a patient cohort of Stavas et al. [12] stands out with a survival rate at 12 months of 41.2%. Local recurrence rate ranged from 18% up to 29%.

2.3. Pooled Data Evaluation

Individual patients' data of three cohorts [12,13,17] met our database assessment protocol and were, therefore, pooled with our single center cohort (n = 71) for further evaluation. After exclusion of palliative radiation with a cumulative radiation dose <30 Gy (EQD2), pooled analysis included a total of 60 patients treated with hypofractionated RT. Median age was 73 (range 49–92) years, 42% showed ECOG ≥2, and 50% of patients presented with distant metastases at initial diagnosis. Furthermore, 60% in the pooled cohort received an EQD2 dose of hypofractionated RT ≥50 Gy. Single dose ranged from 2.50 Gy to 5.00Gy in the pooled patient cohort. Concurrent ChT was administered in 62% of patients and 42% underwent either total or partial thyroidectomy.

Median OS of the pooled patient cohort was 5.3 (range: 1–24, 95% CI: 3472–7128) months. Survival at three, six, and 12 months were 69%, 46%, and 17%, respectively (Figure 3A).

Table 3. Characteristics of patient cohorts and treatment modalities in the systematic review.

Author	Number of Patients (*n*)	Median Age (Years)	Presence of Metastases	Stage Distribution IVA/IVB/IVC (%)	hypoRT in (*n*) Patients	Surgery	ChT	Detailed RT Information
Goutsouliak et al. (2004) [16]	62 referred cases: 57: received radiotherapy, 33 in palliative intention	84 (*n* = 62)	16% (*n* = 62)	NR/NR/16 (*n* = 62)	49	21.0% (*n* = 62)	14.5% (*n* = 62)	(1) *n* = 33: 30 Gy/3 Gy (2) *n* = 8: 50 Gy/2.5 Gy (3) *n* = 5: 40 Gy/2.67 Gy (4) *n* = 2: 45 Gy/2.5 Gy (5) *n* = 1: 45 Gy/3 Gy
Wang et al. (2006) [17]	47: 24 in palliative intention	70.5 (46.1–89.7) (*n* = 24)	25% (IVC)	8/67/25 (*n* = 24)	24	37.5%	16.7%	Median 20 Gy/4Gy (5–40Gy/4Gy)
Stavas et al. (2014) [12]	17	70 (59–84)	47% (*n* = 17)	41/12/47 (*n* = 17) AJCC 7th edition	17	82.4%	88.2%	Median 54Gy/3Gy (40–62.5Gy/2.5–4Gy)
Nachalon et al. (2015) [14]	26 patients: 12 treated in palliative intention	NR	52% (*n* = 23)	NR/NR/52% (*n* = 12)	23	21.7%	47.8%	(1) resectable & ECOG<2: S+RCT 60–70Gy (*n* = 5) (2) non-resect. & ECOG<2: RCT 70Gy (*n* = 6) (3) M+ & ECOG<2: 50Gy (*n* = 9) (4) M+ & ECOG>2: 30Gy (*n* = 3) (5) no treatment (*n* = 3)
So et al. (2017) [15]	30: 18 treated in palliative intention	78 (63–92, *n* = 14)	50% (*n* = 14)	21/29/50 (*n* = 14)	14	28.6%	14.3%	Median 45 Gy/3 Gy (18–45Gy/2.5–6Gy)
Takahashi et al. (2018) [13]	33	71 (49–87) (*n* = 25)	40% (IVC)	19/32/40 (other 1.2%)	25	28.0%	48.0%	Median 50Gy/5Gy (5–60Gy/3–6Gy)

NR = not reported, hypoRT = hypofractionated radiotherapy, IVC = UICC (Union international contre la cancer stage according to 7th edition), ECOG = Eastern Cooperative Oncology Group performance score, AJCC = American Joint Committee on Cancer.

Table 4. Outcome of anaplastic thyroid carcinoma (ATC) patients undergoing hypofractionated radiotherapy (RT).

Author	Median FU (95% CI) in Months	Survival after 3 Months	Survival after 6 Months	Survival after 12 Months	Median Survival (95% CI) in Months
Goutsouliak et al. (2004) [15]	3 (0.6–20)	NR	NR	NR	3 (0.6–20) NR for other hypofractionated treatment modalities
Wang et al. (2006) [16]	4.7 (0.2–114)	54.2%	16.7%	0%	3.2 (0.2–NR, <9)
Stavas et al. (2014) [12]	9.3 (4.6–14)	94.1%	70.6%	41.2%	9.3 (4.6–14)
Nachalon et al. (2015) [14]	6 (2.1–9.8)	NR	NR	NR	6 (2.1–9.8)
So et al. (2017) [17]	3.4 (1.9–4.9)	57.1%	21.4%	7.1%	3.4 (1.9–4.9)
Takahashi et al. (2018) [13]	3 (2.5–3.5)	42.9%	23.8%	4.8%	3 (2.5–3.5)

NR—not reported.

Table 5. Acute Common Terminology Criteria for Adverse Events (CTCAE) and Radiation Therapy Oncology Group (RTOG) ≥ grade 3 adverse events due to the hypofractionated treatment.

Author	CTCAE/RTOG ≥ Grade 3 Events						Local Recurrence
	Dysphagia	Dyspnea	Dysphonia	Mucositis	Dermatitis	Other Symptoms or Supportive Interventions	
Goutsouliak et al. (2004) [15]	NR	NR	NR	NR	NR	NR	NR
Wang et al. (2006) [16]	NR	NR	NR	0	0	4.2% esophagitis	20.1%
Stavas et al. (2014) [12]	24%	NR	NR	NR	24%	18% esophagitis; 23.5% PEG post-RT	18%
Nachalon et al. (2015) [14]	0	0	0	0	0	23%: PEG 35%: tracheostomy	NR
So et al. (2017) [17]	0	0	0	0	0	0	29%
Takahashi et al. (2018) [13]	26%	NR	NR	5%	5%	10% tracheal necrosis & injury to carotid artery	28% 5% died from LR

NR = not reported, PEG = percutaneous endoscopic gastrostomy, LR = local recurrence.

Table 6. Patient and treatment characteristics of pooled patient cohort.

Parameter	*n*
Age, years	
<73	30 (50%)
≥73	30 (50%)
Gender	
Male	31 (52%)
Female	29 (48%)
ECOG-PS	
0–1	35 (58%)
2–4	25 (42%)
UICC stage	
IVA	6 (10%)
IVB	22 (37%)
IVC	30 (50%)
unknown	2 (3%)
EQD2 level	
<50 Gy	24 (40%)
≥50 Gy	36 (60%)
Single dose	
2.5–3.5 Gy	40 (67%)
4–5 Gy	20 (33%)
Concurrent chemotherapy	
No	23 (38%)
Yes	37 (62%)
Treatment	
RT	24 (40%)
CRT	11 (18%)
S + CRT	25 (42%)

ECOG-PS = Eastern Cooperative Oncology Group Performance Score, UICC = Union internationale contre la cancer; IVA/IVB/IVC staging according to 8th edition of UICC, RT = radiation therapy, EQD2 = equivalent dose in 2Gy per fraction, CRT = concurrent chemoradiotherapy, S+CRT = chemoradiotherapy following surgical resection.

In univariate analysis, EQD2 dose in exceed of 50 Gy ($p = 0.014$) and administration of multimodal treatment (surgery and chemoradiotherapy (S + CRT), $p < 0.001$) correlated with an improved OS (Table 7, Figure 3B,C), respectively. A trend for improved survival was found in younger age (<73 age, $p = 0.068$) and a single dose level of 2.5–3.5 Gy ($p = 0.077$). On multivariate analysis, multimodal treatment ($p = 0.003$, hazard ratio [HR]: 0.636, 95% confidence interval [CI]: 0.469–0.861) were significantly associated with an improved OS, whereas a higher EQD2 >50 Gy ($p = 0.065$) did not achieve significance on multivariate analysis.

Table 7. Uni- and multivariate analysis of overall survival (OS) of the pooled patient cohort.

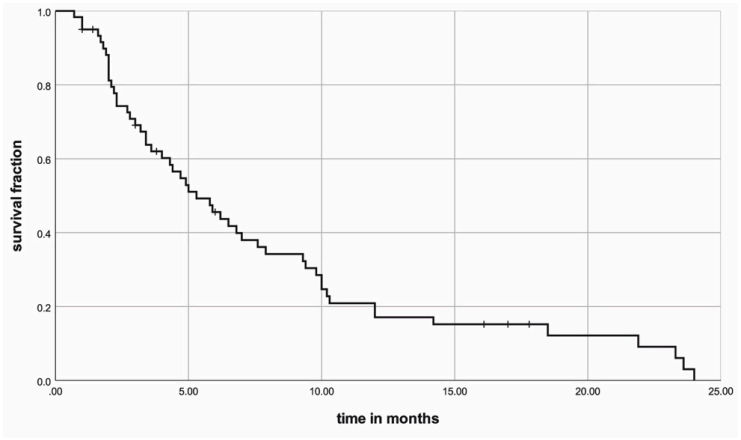
Parameter	At Three Months	At Six Months	At 12 Months	*p*-Value (Univariate Analysis)	*p*-Value (Multivariate Analysis)
Age, years					
<73	77%	58%	19%	0.068	
≥73	62%	35%	15%		
Gender					
Male	76%	50%	8%	0.743	
Female	62%	41%	24%		
ECOG-PS					
0–1	77%	49%	15%	0.95	
2–4	59%	41%	30%		
UICC stage					
IVA/B	74%	51%	25%	0.119	
IVC	67%	42%	11%		
EQD2 level					
<50 Gy	50%	33%	8%	**0.014**	**0.065**
50 Gy	82%	54%	24%		
Single dose					
2.5–3.5 Gy	73%	51%	23%	0.077	
4–5 Gy	62%	34%	6%		
Concurrent chemotherapy					
No	73%	44%	11%	0.286	
Yes	67%	47%	20%		
Treatment					
RT/CRT	52%	24%	12%	**<0.001**	**0.003**
S+CRT	92%	68%	32%		

ECOG-PS = Eastern Cooperative Oncology Group Performance Score, UICC = Union internationale contre la cancer; IVA/IVB/IVC staging according to 8th edition of UICC, RT = radiation therapy, EQD2 = equivalent dose in 2Gy per fraction, CRT = concurrent chemoradiotherapy, S+CRT = chemoradiotherapy following surgical resection.

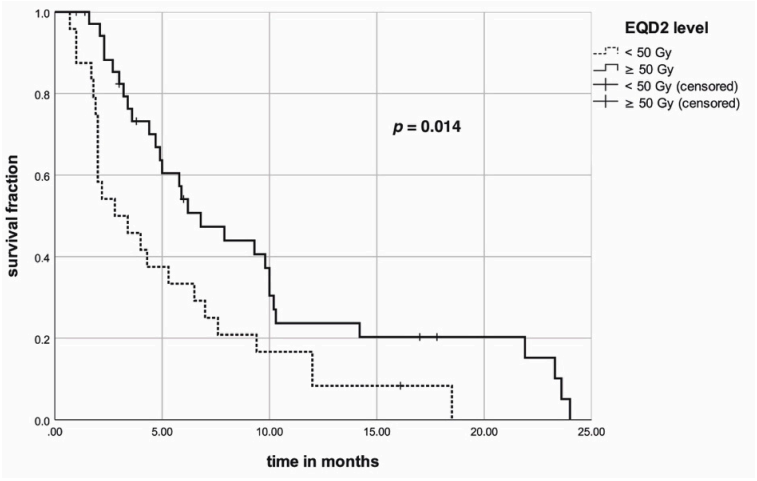
2.4. Propensity Score Matching (PSM)

Individual patients´ data of three cohorts [12,13,17] met our database assessment protocol, and our single center cohort were included in the propensity score matching (PSM) analysis. Normofractionated RT was defined as a single dose of less than 2.5 Gy and hypofractionated RT with ≥2.50 Gy. Patients receiving palliative radiation with ≤30 Gy were excluded from evaluation. Patients treated with normofractionated RT were matched in a 1:2 ratio to patients treated hypofractionated RT. To each patient treated with normofractionated RT, two corresponding patients with exactly the same ECOG PS and gender were matched. PSM also considered age and treatment mode. Eighteen normofractionated patients were matched to 36 hypofractionated patients (Table 8). In the normofractioanted subgroup, 83% of all patients were treated with a single dose of 2 Gy and the median cumulative radiation was 60 Gy (range: 44–71, EQD2). In the hypofractionated subgroup, median cumulative radiation dose was 55 Gy (range: 33–65, EQD2).

A.



B.



C.

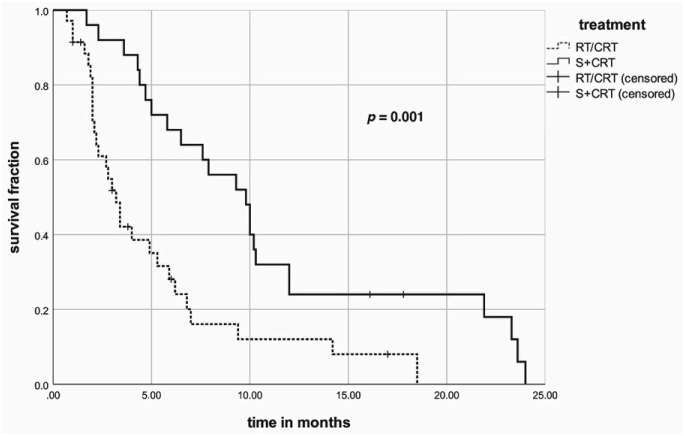


Figure 3. (**A**) Kaplan–Meier curve for overall survival of pooled patient cohort. (**B**) Kaplan–Meier curves concerning EQD2 level for overall survival of pooled patient cohort. The *p*-value was calculated with the log-rank test. (**C**) Kaplan–Meier curves concerning multimodal treatment for overall survival of pooled patient cohort. The *p*-value was calculated with the log-rank test.

Table 8. Patient and treatment characteristics of propensity score matching (PSM) cohort.

Parameter	Entire PSM-Cohort N (%)	Normofractionated Subgroup N (%)	Hypofractionated Subgroup N (%)	*p*-Value
Total	54 (100)	18 (33)	36 (67)	
Age, years (range)	70 (54–86)	68 (55–83)	71 (54–86)	0.235
Gender				
Male	27 (50)	9 (50)	18 (50)	0.999
Female	27 (50)	9 (50)	18 (50)	
ECOG				
0–1	48 (89)	16 (89)	42 (89)	0.999
2–4	6 (11)	2 (11)	4 (11)	
UICC stage				
IVA	4 (10)	2 (11)	2 (6)	
IVB	23 (37)	13 (72)	10 (28)	**0.002**
IVC	26 (50)	3 (17)	23 (64)	
EQD2 level				
<50 Gy	14 (26)	2 (11)	12 (33)	0.082
≥50 Gy	40 (74)	16 (89)	24 (67)	
Concurrent chemotherapy				
No	18 (33)	6 (33)	12(33)	0.999
Yes	36 (67)	12 (67)	24 (67)	
Treatment				
RT/CRT	26 (48)	6 (33)	20 (56)	0.128
S+CRT/RT	28 (52)	12 (67)	16 (45)	

Median OS of the entire PSM cohort was seven months (range: 1–33) with six, 12, and 24 months survival rates of 55%, 20%, and 3%. Median OS of the normofractionated RT subgroup was eight months (range: 1–33) with six, 12, and 24 months survival rates of 61%, 17%, and 8%. Median OS of the hypofractionated RT subgroup was seven months (range: 1–24) with six, 12, and 24 months survival rates of 52%, 21%, and 0%. Fractionation regimen achieved no significance ($p = 0.372$) in univariate analysis for OS (Figure 4).

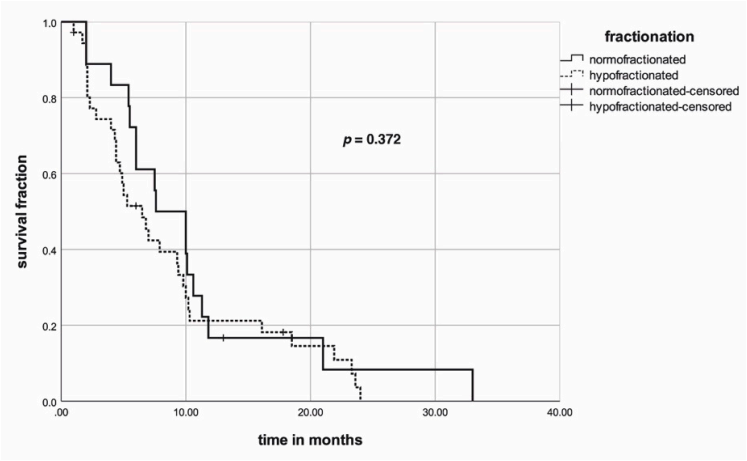


Figure 4. Kaplan–Meier curves concerning fractionation regimen for overall survival of PSM cohort. The *p*-value was calculated with the log-rank test.

3. Discussion

We report on the utilization of hypofractionated RT in a pooled patient cohort of 71 patients with ATC. To our knowledge, this is one of the largest studies reported to date, evaluating hypofractionated RT that was defined as a single dose per fraction ≥2.5 Gy [12,13,17].

The outcomes concerning OS and treatment-related toxicity reported in our pooled analysis are consistent with previous reports, with the majority of ATC patients presenting with symptomatic or metastatic disease. Improved OS in our cohort was observed in patients receiving multimodal treatment ($p = 0.006$) and male patients ($p = 0.04$). Administering ChT concurrent to hypofractionated RT showed a survival benefit of more than 30% at 12 months but was not an independent predictor ($p = 0.327$). The results of the pooled data analysis suggest that a total dose of EQD2 ≥50 Gy ($p = 0.014$) and multimodal treatment ($p < 0.001$) correlate with longer survival and, hence, are crucial for favorable OS.

When applied in ATC, conventional RT has been shown to provide symptom palliation with similar outcomes compared to conventional RT regarding local control [6,12,13,17]. In this context, Oweida et al. [11] investigated radiosensitivity toward hypofractionated RT of human ATC cell lines in an orthotopic mouse model [11,18] following the in vitro characterization of the levels of radiosensitivity based on genetic profiling of the ATC cell lines. The definition of hypofractionated RT at ≥2.5 Gy per fraction is aligned with our treatment protocol. A 51.8-fold decrease in local tumor growth ($p = 0.0097$) assessed by average photon radiance ($p = 0.0094$) in vivo at day 36 was reported in that study compared to the control, whereas conventional RT showed a 6.7-fold decrease ($p = 0.0057$), respectively. In addition, hypofractionated RT treated mice had significantly longer OS than conventionally irradiated mice (HR = 6.049, 95% CI 1.863–28.05, $p < 0.001$) and a decreased rate of pulmonary metastases ($p < 0.001$), resulting in a strong preclinical rationale for the utilization of hypofractionated RT concepts.

To date, however, the use of hypofractionated RT in the treatment for ATC remains highly controversial. It is still mostly administered in palliative setting with a common cumulative dose ≤30 Gy [6]. Despite extensive research, studies comparing differently fractionated RT regimens for ATC are not available. For this purpose, we have investigated hypofractionation as an integral part of ATC treatment. Due to its rapid progression and the early onset of metastatic disease, management of ATC patients requires a multimodal approach including surgical resection of the primary tumor followed by chemoradiation [5–7].

The most recent study on ATC of Fan et al. [19] provided a comprehensive retrospective analysis of different outcomes in 104 ATC patients treated in a multimodal approach, which was administered to a total of 51% of patients and had a significant association ($p = 0.017$) with a decreased risk of local disease progression, but no association with OS was found. Multimodal treatment approaches such as surgery followed by concurrent chemoradiotherapy have been shown to be significantly relevant for the beneficial OS as an independent predictor by Glaser et al. [20]. Similar findings were reported by several authors [12,20–23] and may be attributable to lower recurrence rate [24] and a decrease in local complication rate caused by impending of trachea or damage to esophagus and carotid artery [23,25]. Our single center data as well as our pooled analysis supports the multimodal treatment approach ($p = 0.006$, $p < 0.001$).

However, normofractionated RT remains the standard care in these studies, and data evaluating other fractionation regimens such as hypofractionation are limited [20–23,26]. Conversely, studies gathered by systematic review investigated the integration of hypofractionation into the treatment. Nachalon et al. [14] investigated hypofractionated RT in 23 patients with ATC (surgical resection performed in 22%) and reported ChT to have a significant effect on survival ($p = 0.01$; administered to 48% of all patients). Stavas et al. [12] applied hypofractionated RT to 17 ATC patients in combination with surgery (82%) and ChT (88%-paclitaxel with or without carboplatin). Notably, Stavas et al. [12] and Nachalon et al. [14] do also stand out with their reported survival rates of 9.3 (range: 4.6–14) and 6 (range 2.1–9.8) months, respectively. These OS-rates are comparable to what has been reported for the entire cohort by e.g., Fan et al. [19] (seven months: 95%; CI: 4.5–9.5 months), where hyperfractionation

and conventional fractionation regimens were used instead. Therefore, integration of hypofractionated RT into multimodal treatment could be considered for patients with ATC.

Apart from multimodal approaches, one of the crucial findings concerning radiotherapy for ATC was a significant dose-response relation [20,26,27]. Wendler et al. [26] showed the dose-response relation in a multi-center study for a cohort consisting of 100 patients with a total EBRT > 40 Gy (HR = 0.34, 95% CI 0.15–0.76, $p = 0.008$).

Large-scale analyses of patients from National Cancer Data Base by Glaser et al. [20] or Pezzi et al. [27] showed improved OS to be associated with high-dose RT in exceed of 59.3 Gy (HR = 0.67, $p < 0.005$) and 59 Gy ($p = 0.008$), respectively. These results are comparable to our findings in both, single center and pooled data evaluation with an EQD2 > 50 Gy being associated with longer OS. Importantly, data of Nachalon et al. [14] on the beneficial outcome of ATC patients treated with hypofractionated RT in curative intention ($p < 0.001$) possibly implies comparable dose-response relation given different irradiation dosages of the gross tumors (70 Gy vs. 50–63 Gy vs. <30 Gy). Nevertheless, decisions for specific treatments were made based on individual characteristics of patients, including performance status, disease progression and resectability. Compared to our data, Takahashi et al. [13] similarly reported a total dose of >50 Gy ($p = 0.049$) to correlate with longer OS in the univariate analysis. In order to compare normofractionated to hypofractionated RT, we performed a PSM analysis based on the same database assessment protocol with a 1:2 matching. After exclusion of palliative treatment and adjustment for performance status and gender, hypofractionated RT appears to be non-inferior to normofractionated RT concerning OS. Although, ATC is thought to be relatively radioresistant, treatment response could be achieved with sufficient cumulative radiation doses using hypofractioned regimes.

Development of distant metastases is a common part of disease progression in patients with ATC and can thus be a limiting factor for therapy related decisions. It is considered a significant risk factor for the survival [28]. Correspondingly, Stavas et al. [12] demonstrated a difference in the median OS for those patients with and without distant metastases (6.4 months vs. 14.2 months), respectively. This is also comparable with the results on metastatic status that were found in the studies mentioned previously [20,21,26,27]. In contrast, however, Wang et al. [16] and our study found no impact of TNM stage on progression-free survival or OS.

In addition, Quality of life (QoL) remains one the most important therapy goals in ATC and sufficient palliation of symptoms impacts OS and PFS. Indeed, Sugitani et al. [28] evaluated 677 patients with ATC from 38 different institutions and identified presence of acute local symptoms, such as severe dysphonia, dysphagia, dyspnea, and progressive tumor growth <1 month ($p = 0.0014$), as significant risk for shorter OS in both univariate and multivariate analysis. Correspondingly, hypofractionation was reported to achieve local control in 71% of patients in an Australian study of So et al. [17]. It was administered to a cohort of 14 patients, who had a distant metastatic disease in 50%. In total, several studies [12,13,16,17] gathered by systematic review showed that hypofractionation can sufficiently provide an acceptable local control rate of 71–82% at the time of the last follow-up or death. This is comparable to the study mentioned previously [19] and not inferior to the results of single or combined modality treatment of Veness et al. [29]. In our study, however, we found no local progression during RT or within follow-up (≤12 months).

Based on our data, irradiation with higher dosages per single fraction over a shorter period of time is sufficient to effectively reduce primary tumor volume. Importantly, radiotherapy-induced acute and late toxicities need to be considered using alternative fractionation regimens [30]. We found a manageable treatment-related toxicity of hypofractionated RT in our single center cohort as well as studies included into systematic review [12–14,16,17]. These results, especially of Stavas et al. [12], are similar to our single center data and seem to have more tolerable toxicity profiles than in the previously mentioned studies. On the contrary, toxicity rates obtained in the study of Takahashi et al. [13] excel across the studies included in the systematic review. The authors used an ultra-hypofractionated RT in ATC patients with a median dose per fraction of 5 Gy [13]. Therefore, patients in that study

developed acute grade 3 dysphagia, mucositis, and dermatitis in 26%, 5%, and 5% of cases, respectively, in the hypofractionated RT group (n = 19), but also one case of grade 4 toxicity due to the injury of trachea and one case of grade 5 injury of carotid artery (18%) were reported. We found that hypofractionated RT (≥4Gy/fr) is not beneficial for OS compared to moderate hypofractionated RT. Importantly, RT with a single dose of 2.50 to 3.50 Gy per fraction shows a trend of more favorable survival compared with ≥4 Gy (12-month survival rate of 23 versus 6%, $p = 0.077$). Currently, the extent to which ultra-hypofractionation is associated with greater toxicity rates is controversial, as it has been reported for several other cancer subtypes [31].

Historically, hyperfractionated RT was considered as an alternative to normo- or hypofractionated RT regimen [32]. Dandekar et al. [10] treated 39 patients (80% with ATC) with hyperfractionated RT and were confronted with higher toxicity rates, when compared to our results: 38%, 12%, 30%, and 30% of grade 3 erythema, desquamation, dysphagia and esophagitis were reported. Respectively, grade 4 toxicity was reported in for 18%, 9%, 44%, and 47% of cases (n = 34/39). In addition, local control (complete/partial response and stable disease) was reported in a total of 85% of patients in that research group, which is comparable to the reported results of studies from our systematic review.

With respect to the pathogenesis of radiation-induced toxicities, irradiation dosage may not be the only influence on the rate of adverse events [30]. The actual irradiation technique impacts radiation-induced acute and late toxicities. E.g., IMRT is reported to be safer by delivering higher doses of irradiation (66 Gy vs. 60 Gy 3D-CRT, $p = 0.005$) with a better homogeneity than 3D-CRT, sparing high-risk regions (e.g. salivary gland, myelon) and to have a beneficial impact on OS and progression-free survival (PFS) (OS: HR = 0.30, $p = 0.005$; PFS: HR = 0.33, $p = 0.005$) [33]. Potential escalations are therefore possible because of a lower rate on severe toxicities—a total of 2 patients was reported to develop CTCAE Grade 3 dermatitis after IMRT by Park et al. [33]. In our study, however, IMRT technique did not achieve significance for beneficial OS in the univariate analysis ($p = 0.701$).

Several limitations must be considered for our study such as the retrospective nature and, therefore, a risk of including hidden selection biases. Despite the small patient numbers and long recruiting time in our single center cohort, our pooled analysis remains one of the largest studies reported to date.

Hypofractionated RT shows manageable toxicity with acceptable local control even in dose-escalated regimens. Further prospective studies need to address hypofractionated RT in the context of multimodal treatment of ATC.

4. Patients and Methods

4.1. Single Center Evaluation

The study was ethically approved by the Institutional Review Board (IRB) of Ludwig-Maximilians University in Munich, Germany (approval number: 20-023). All consecutive patients with histologically confirmed ATC irradiated between 2009 and 2019 were evaluated. Hypofractionated RT to the primary tumor was defined as an irradiation with a single dose of 2.5 Gy or more. Patients receiving palliative radiation with a cumulative dose of ≤30 Gy were excluded. As a result, 11 (32%) patients were irradiated with a hypofractionated regimen and included in the single center cohort (Table 1).

4.2. Systematic Review of Literature

A complete literature search was conducted using MEDLINE/Pubmed (National Center for Biotechnology Information, Bethesda, MD, USA) and Cochrane databases on 15 February 2020 in order to identify relevant publications. The search strategy for MEDLINE/PubMed with Boolean operators and applied terms is illustrated in Table 9. All Cochrane reviews concerning ATC were evaluated on 25 February 2020. Data analysis was conducted within a timeframe from 25 February to 2 March 2020.

Table 9. Search terms used for PubMed/MEDLINE database search.

	Term	Studies Identified
1	(Radiotherapy or radiotherap* or radio-therap* or irradiation or irradiat* or re-irradiat* or reirradiat*)	530,114
2	("anaplastic thyroid cancer" or "anaplastic thyroid carcinoma" or ATC)	4658
3	1 and 2	333
4	"2000/01/01" [PDat]: "2019/12/01" [PDat]	267

Retrospective studies and prospective clinical trials dated from 1 January 2000 to 1 December 2019, written in English and containing search terms shown in Table 9 were included preliminarily. Abstracts were analyzed for eligibility based on irradiation dosage ≥2.5 Gy or hypofractionated RT in palliative or curative situation of ATC. Data regarding performance status and toxicity were extracted and analyzed, if available. Identified systematic reviews meeting search criteria were examined for relevant publications.

Publications reporting RT with a single dose less than 2.5 Gy per fraction were excluded. Pre-clinical in vitro and in vivo studies, drug trials, guidelines, consortia, duplicates, case-reports, and publications without exact specification of fractionation regimen or reviews were excluded. Studies providing no extractable data for groups treated with hypofractionated RT or reporting groups with a lower range of dose per fraction of less than 2.5 Gy were excluded. Flow-chart of literature reviewing process is shown in Figure 2.

4.3. Pooled Analysis and Data Management

Eligible publications providing raw data on performance status, disease progression and stage, therapeutic modality, irradiation dosage and OS were extracted and pooled with our single center cohort in order to examine patient characteristics, treatment and outcomes of patients with ATC. Hypofractionated RT was redefined for raw data as ≥2.5 Gy per fraction, thus, aligning treatment specification with the patient cohort and the setting described above. Patients receiving palliative radiation doses with ≤30 Gy (EQD2) were excluded.

Statistical analyses were performed using SPSS statistics 25 (IBM, Chicago, IL, USA). Subgroups were compared using the log-rank test. All significant variables in univariate analysis were included in a multivariate Cox regression analysis. The proportional hazard assumption of the Cox regression analysis was tested. OS was defined as the time between the diagnosis of ATC and death. Patients still alive or lost to follow-up were censored at last visit. For all statistical analyses, a significance level of $\alpha = 0.05$ was defined.

5. Conclusions

Hypofractionated RT appears to achieve sufficient local control with acceptable toxicity. Multimodal treatment and dose escalation (≥50 Gy) are important prognostic factors in patients receiving hypofractioned RT in our single-center cohort and pooled analysis. Hypofractionated radiotherapy appears to be non-inferior compared to normofractionated RT concerning OS. Hypofractioned RT could be an integral part of multimodal treatment and should be investigated in further studies.

Author Contributions: Conceptualization, L.K., D.O., and T.A.; methodology, L.K., C.S., C.B., and D.O.; software, L.K. and D.O.; validation, L.K., D.O., and T.A.; formal analysis, L.K. and D.O.; investigation, D.O., T.A. and L.K.; resources, L.K., C.S., C.B., and J.R.; data curation, L.K., C.B., C.S., and J.R.; writing—original draft preparation, D.O. and L.K.; writing—review and editing, C.S., C.B., L.K., V.F.K., J.R., T.A., and D.O.; visualization, L.K. and D.O.; supervision, C.B., C.S., and L.K.; project administration, C.B., C.S., and L.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Dal Maso, L.; Tavilla, A.; Pacini, F.; Serraino, D.; van Dijk, B.A.C.; Chirlaque, M.D.; Capocaccia, R.; Larrañaga, N.; Colonna, M.; Agius, D.; et al. Survival of 86,690 patients with thyroid cancer: A population-based study in 29 European countries from EUROCARE-5. *Eur. J. Cancer* **2017**, *77*, 140–152. [CrossRef] [PubMed]
2. Neff, R.L.; Farrar, W.B.; Kloos, R.T.; Burman, K.D. Anaplastic Thyroid Cancer. *Endocrinol. Metab. Clin. N. Am.* **2008**, *37*, 525–538. [CrossRef] [PubMed]
3. Xu, B.; Fuchs, T.L.; Dogan, S.; Landa, I.; Katabi, N.; Fagin, J.A.; Tuttle, R.M.; Sherman, E.J.; Gill, A.J.; Ghossein, R. Dissecting Anaplastic Thyroid Carcinoma (ATC): A Comprehensive Clinical, histologic, Immunophenotypic, and Molecular Study of 360 Cases. *Thyroid* **2020**. [CrossRef] [PubMed]
4. Yoo, S.-K.; Song, Y.S.; Lee, E.K.; Hwang, J.; Kim, H.H.; Jung, G.; Kim, Y.A.; Kim, S.; Cho, S.W.; Won, J.-K.; et al. Integrative analysis of genomic and transcriptomic characteristics associated with progression of aggressive thyroid cancer. *Nat. Commun.* **2019**, *10*, 2764. [CrossRef] [PubMed]
5. Haddad, R.I.; Nasr, C.; Bischoff, L.; Busaidy, N.L.; Byrd, D.; Callender, G.; Dickson, P.; Duh, Q.-Y.; Ehya, H.; Goldner, W.; et al. NCCN Guidelines Insights: Thyroid Carcinoma, Version 2.2018. *J. Natl. Compr. Cancer Netw.* **2018**, *16*, 1429–1440. [CrossRef]
6. Filetti, S.; Durante, C.; Hartl, D.; Leboulleux, S.; Locati, L.D.; Newbold, K.; Papotti, M.G.; Berruti, A. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **2019**, *30*, 1856–1883. [CrossRef]
7. Smallridge, R.C.; Ain, K.B.; Asa, S.L.; Bible, K.C.; Brierley, J.D.; Burman, K.D.; Kebebew, E.; Lee, N.Y.; Nikiforov, Y.E.; Rosenthal, M.S.; et al. American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer. *Thyroid* **2012**, *22*, 1104–1139. [CrossRef]
8. Vulpe, H.; Kwan, J.Y.Y.; McNiven, A.; Brierley, J.D.; Tsang, R.; Chan, B.; Goldstein, D.P.; Le, L.W.; Hope, A.; Giuliani, M. Patterns of failure in anaplastic and differentiated thyroid carcinoma treated with intensity-modulated radiotherapy. *Curr. Oncol.* **2017**, *24*, 226. [CrossRef]
9. Caudell, J.J.; Ward, M.C.; Riaz, N.; Zakem, S.J.; Awan, M.J.; Dunlap, N.E.; Isrow, D.; Hassanzadeh, C.; Vargo, J.A.; Heron, D.E.; et al. Volume, Dose, and Fractionation Considerations for IMRT-based Reirradiation in Head and Neck Cancer: A Multi-institution Analysis. *Int. J. Radiat. Oncol.* **2018**, *100*, 606–617. [CrossRef]
10. Dandekar, P.; Harmer, C.; Barbachano, Y.; Rhys-Evans, P.; Harrington, K.; Nutting, C.; Newbold, K. Hyperfractionated Accelerated Radiotherapy (HART) for Anaplastic Thyroid Carcinoma: Toxicity and Survival Analysis. *Int. J. Radiat. Oncol.* **2009**, *74*, 518–521. [CrossRef]
11. Oweida, A.; Phan, A.; Vancourt, B.; Robin, T.; Hararah, M.K.; Bhatia, S.; Milner, D.; Lennon, S.; Pike, L.; Raben, D.; et al. Hypofractionated Radiotherapy Is Superior to Conventional Fractionation in an Orthotopic Model of Anaplastic Thyroid Cancer. *Thyroid* **2018**, *28*, 739–747. [CrossRef] [PubMed]
12. Stavas, M.J.; Shinohara, E.T.; Attia, A.; Ning, M.S.; Friedman, J.M.; Cmelak, A.J. Short Course High Dose Radiotherapy in the Treatment of Anaplastic Thyroid Carcinoma. *J. Thyroid Res.* **2014**, *2014*, 1–7. [CrossRef] [PubMed]
13. Takahashi, N.; Matsushita, H.; Umezawa, R.; Yamamoto, T.; Ishikawa, Y.; Katagiri, Y.; Tasaka, S.; Takeda, K.; Fukui, K.; Kadoya, N.; et al. Hypofractionated Radiotherapy for Anaplastic Thyroid Carcinoma: 15 Years of Experience in a Single Institution. *Eur. Thyroid J.* **2019**, *8*, 24–30. [CrossRef] [PubMed]
14. Nachalon, Y.; Stern-Shavit, S.; Bachar, G.; Shvero, J.; Limon, D.; Popovtzer, A. Aggressive Palliation and Survival in Anaplastic Thyroid Carcinoma. *JAMA Otolaryngol. Neck Surg.* **2015**, *141*, 1128. [CrossRef] [PubMed]
15. Goutsouliak, V.; Hay, J.H. Anaplastic thyroid cancer in British Columbia 1985–1999: A population-based study. *Clin. Oncol.* **2005**, *17*, 75–78. [CrossRef] [PubMed]
16. Wang, Y.; Tsang, R.; Asa, S.; Dickson, B.; Arenovich, T.; Brierley, J. Clinical outcome of anaplastic thyroid carcinoma treated with radiotherapy of once- and twice-daily fractionation regimens. *Cancer* **2006**, *107*, 1786–1792. [CrossRef] [PubMed]
17. So, K.; Smith, R.E.; Davis, S.R. Radiotherapy in anaplastic thyroid carcinoma: An Australian experience. *J. Med. Imaging Radiat. Oncol.* **2017**, *61*, 279–287. [CrossRef]

18. Morrison, J.A.; Pike, L.A.; Lund, G.; Zhou, Q.; Kessler, B.E.; Bauerle, K.T.; Sams, S.B.; Haugen, B.R.; Schweppe, R.E. Characterization of Thyroid Cancer Cell Lines in Murine Orthotopic and Intracardiac Metastasis Models. *Horm. Cancer* **2015**, *6*, 87–99. [CrossRef]
19. Fan, D.; Ma, J.; Bell, A.C.; Groen, A.H.; Olsen, K.S.; Lok, B.H.; Leeman, J.E.; Anderson, E.; Riaz, N.; McBride, S.; et al. Outcomes of multimodal therapy in a large series of patients with anaplastic thyroid cancer. *Cancer* **2020**, *126*, 444–452. [CrossRef]
20. Glaser, S.M.; Mandish, S.F.; Gill, B.S.; Balasubramani, G.K.; Clump, D.A.; Beriwal, S. Anaplastic thyroid cancer: Prognostic factors, patterns of care, and overall survival: Anaplastic Thyroid Cancer. *Head Neck* **2016**, *38*, E2083–E2090. [CrossRef]
21. Kim, T.Y.; Kim, K.W.; Jung, T.S.; Kim, J.M.; Kim, S.W.; Chung, K.-W.; Kim, E.Y.; Gong, G.; Oh, Y.L.; Cho, S.Y.; et al. Prognostic factors for Korean patients with anaplastic thyroid carcinoma. *Head Neck* **2007**, *29*, 765–772. [CrossRef]
22. Lee, D.Y.; Won, J.-K.; Lee, S.-H.; Park, D.J.; Jung, K.C.; Sung, M.-W.; Wu, H.-G.; Kim, K.H.; Park, Y.J.; Hah, J.H. Changes of Clinicopathologic Characteristics and Survival Outcomes of Anaplastic and Poorly Differentiated Thyroid Carcinoma. *Thyroid* **2016**, *26*, 404–413. [CrossRef] [PubMed]
23. Haigh, P.I.; Ituarte, P.H.G.; Wu, H.S.; Treseler, P.A.; Posner, M.D.; Quivey, J.M.; Duh, Q.Y.; Clark, O.H. Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. *Cancer* **2001**, *91*, 2335–2342. [CrossRef]
24. Lee, D.Y.; Won, J.-K.; Choi, H.S.; Park, D.J.; Jung, K.C.; Sung, M.-W.; Kim, K.H.; Hah, J.H.; Park, Y.J. Recurrence and Survival After Gross Total Removal of Resectable Undifferentiated or Poorly Differentiated Thyroid Carcinoma. *Thyroid* **2016**, *26*, 1259–1268. [CrossRef] [PubMed]
25. Are, C.; Shaha, A.R. Anaplastic Thyroid Carcinoma: Biology, Pathogenesis, Prognostic Factors, and Treatment Approaches. *Ann. Surg. Oncol.* **2006**, *13*, 453–464. [CrossRef] [PubMed]
26. Wendler, J.; Kroiss, M.; Gast, K.; Kreissl, M.C.; Allelein, S.; Lichtenauer, U.; Blaser, R.; Spitzweg, C.; Fassnacht, M.; Schott, M.; et al. Clinical presentation, treatment and outcome of anaplastic thyroid carcinoma: Results of a multicenter study in Germany. *Eur. J. Endocrinol.* **2016**, *175*, 521–529. [CrossRef]
27. Pezzi, T.A.; Mohamed, A.S.R.; Sheu, T.; Blanchard, P.; Sandulache, V.C.; Lai, S.Y.; Cabanillas, M.E.; Williams, M.D.; Pezzi, C.M.; Lu, C.; et al. Radiation therapy dose is associated with improved survival for unresected anaplastic thyroid carcinoma: Outcomes from the National Cancer Data Base: Unresected Anaplastic Thyroid Carcinoma. *Cancer* **2017**, *123*, 1653–1661. [CrossRef]
28. Sugitani, I.; Miyauchi, A.; Sugino, K.; Okamoto, T.; Yoshida, A.; Suzuki, S. Prognostic Factors and Treatment Outcomes for Anaplastic Thyroid Carcinoma: ATC Research Consortium of Japan Cohort Study of 677 Patients. *World J. Surg.* **2012**, *36*, 1247–1254. [CrossRef]
29. Veness, M.J.; Porter, G.S.; Morgan, G.J. Anaplastic thyroid carcinoma: dismal outcome despite current treatment approach. *ANZ J. Surg.* **2004**, *74*, 559–562. [CrossRef]
30. De Ruysscher, D.; Niedermann, G.; Burnet, N.G.; Siva, S.; Lee, A.W.M.; Hegi-Johnson, F. Radiotherapy toxicity. *Nat. Rev. Dis. Primer* **2019**, *5*, 13. [CrossRef]
31. Teckie, S.; Lok, B.H.; Rao, S.; Gutiontov, S.I.; Yamada, Y.; Berry, S.L.; Zelefsky, M.J.; Lee, N.Y. High-dose hypofractionated radiotherapy is effective and safe for tumors in the head-and-neck. *Oral Oncol.* **2016**, *60*, 74–80. [CrossRef] [PubMed]
32. Moulder, J.E.; Seymour, C. Radiation fractionation: the search for isoeffect relationships and mechanisms. *Int. J. Radiat. Biol.* **2018**, *94*, 743–751. [CrossRef] [PubMed]
33. Park, J.W.; Choi, S.H.; Yoon, H.I.; Lee, J.; Kim, T.H.; Kim, J.W.; Lee, I.J. Treatment outcomes of radiotherapy for anaplastic thyroid cancer. *Radiat. Oncol. J.* **2018**, *36*, 103–113. [CrossRef] [PubMed]

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

6. Paper II

Journal of
Clinical Medicine

MDPI

Article

Clinical Outcome and Toxicity in the Treatment of Anaplastic Thyroid Cancer in Elderly Patients

Teresa Augustin [1], Dmytro Oliinyk [1], Viktoria Florentine Koehler [2], Josefine Rauch [1], Claus Belka [1,3], Christine Spitzweg [2,3] and Lukas Käsmann [1,3,*]

[1] Department of Radiation Oncology, University Hospital, LMU Munich, 80539 Munich, Germany; teresa.augustin@med.uni-muenchen.de (T.A.); dmytro.oliinyk@med.uni-muenchen.de (D.O.); josefine.rauch@med.uni-muenchen.de (J.R.); claus.belka@med.uni-muenchen.de (C.B.)
[2] Department of Internal Medicine IV, University Hospital, LMU Munich, 80539 Munich, Germany; viktoria.koehler@med.uni-muenchen.de (V.F.K.); christine.spitzweg@med.uni-muenchen.de (C.S.)
[3] German Cancer Consortium (DKTK), Partner Site Munich, 81377 Munich, Germany
* Correspondence: lukas.kaesmann@med.uni-muenchen.de; Tel.: +49-894-400-74511

Received: 1 September 2020; Accepted: 3 October 2020; Published: 9 October 2020

Abstract: Background: The present study aims to evaluate the outcomes and toxicity of elderly anaplastic thyroid cancer (ATC) patients receiving (chemo)radiotherapy, as well as to identify prognostic factors. Patients and methods: A systematic review using the MEDLINE/PubMed and Cochrane databases was performed. Individual data from all eligible studies were extracted, and a pooled analysis (n = 186) was conducted to examine patient characteristics and treatment. All consecutive ATC patients (≥65 years) treated between 2009 and 2019 at our institution were evaluated for outcomes concerning progression-free survival (PFS), overall survival (OS) probabilities and treatment-related toxicity. Results: The systematic review and pooled analysis identified age as a prognostic factor. The median OS of our patient cohort (n = 26) was three months (range = 0–125). The 6-, 12- and 24-month survival rates were 35%, 22% and 11%, respectively. In the univariate analysis, a Karnofsky performance status of >70%, the Union for International Cancer Control Tumor–Node–Metastasis classification, multimodal therapy and an EQD2 of >49 Gy were correlated with longer OS and PFS. The acute grade 3 toxicity of dysphagia, dyspnea, dermatitis, mucositis and dysphonia was found in 23%, 15%, 12%, 12% and 8% of patients. Conclusion: Age appears to be a prognostic factor in ATC. Elderly ATC patients can tolerate multimodal treatment and achieve a promising outcome. Prospective studies need to confirm our findings.

Keywords: ATC; anaplastic thyroid cancer; elderly; irradiation; survival

1. Introduction

Anaplastic thyroid cancer (ATC) is one of the rarest, yet one of the most lethal, carcinomas that is seen in the human body. It only accounts for 1–2% [1–4] of all known thyroid carcinomas per year; however, it is responsible for about 50% of thyroid-cancer-associated deaths [2,4,5]. Its aggressive growth leads to the rapid infiltration of vital adjacent organs, such as the trachea, larynx and esophagus, as well as neck vessels, nerves and muscles. Additionally, early metastases commonly to lung and bones [6–9] result in fatal outcomes with a median overall survival (OS) that ranges between three and six months [10]. The overall one-year survival rate is only 10–20% [1,4,5,11–14].

The optimal treatment of ATC remains unknown. Due to its low incidence, large prospective trials are rarely performed. However, several studies propose a multimodal therapy regime, consisting of radical resection, radiotherapy and chemotherapy, to improve outcomes in ATC patients [3,11,13–15]. Despite this, survival has remained relatively stable over the past decades [2], especially in elderly

patients, who make up an important subgroup of ATC patients, among which prognosis is very poor [3,4,12,15–18]. This group of people often represents a combination of several comorbidities, immunodeficiencies and organ dysfunctions and may not tolerate aggressive treatment [19,20]. In contrast, elderly patients with a poor prognosis should spend as little of their remaining lifetime attending oncologic treatments and are, therefore, better candidates for short treatments including hypofractionated radiotherapy [21]. These considerations mean that it is important to judge a patient's survival time as accurately as possible to personalize treatment approaches.

We aim to perform a systematic review using the MEDLINE/PubMed and Cochrane databases to evaluate patients' age as a prognostic factor. Individual data from all eligible studies will be extracted and pooled in order to examine patient characteristics and treatment. Furthermore, all consecutive ATC patients ≥ 65 years at initial diagnosis will be investigated concerning outcome and treatment-related toxicity and prognostic factors of OS and progression-free survival (PFS) will be identified.

2. Patients and Methods

2.1. Systematic Review of Literature

A systematic review of the literature was undertaken using PubMed/MEDLINE and Cochrane databases following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) protocol. Abstracts were screened for eligibility so that the most important articles were analyzed by full-text screening. Inclusion criteria were based on the study setting. Age was investigated as one of the prognostic factors in the uni-/multivariate analyses. Furthermore, treatment specifications and cut-off values for age of included studies were analyzed. Reviews, case reports, experimental data, personalized treatments, drug trials or publications arising conflict of interests were excluded.

2.2. Pooled Analysis

Eligible publications providing raw data on age, TNM/UICC stage distribution, treatment (e.g., surgery, radiotherapy, chemotherapy) and outcome were extracted and evaluated in order to examine patient- and treatment-related characteristics as well as the outcomes of ATC patients.

Statistical analyses were performed using SPSS statistics 25 (IBM, Chicago, IL, USA). Subgroups were compared using the log-rank test. For all statistical analyses, a significance level of $\alpha = 0.05$ was defined.

2.3. Single-Center Patient Cohort

The retrospective study included data from 26 consecutive patients diagnosed with ATC between 2009 and 2019 at our center. The study protocol was approved by the ethics committee of the Ludwig Maximilian University of Munich (Munich, Germany) (Approval Number: 19–885).

2.4. Data Acquisition

Data were analyzed according to ten patient- and treatment-related characteristics: age, gender, Karnofsky performance status (KPS), the Union for International Cancer Control classification (UICC stage), nodal involvement, distant metastases, radiation technique, performance of surgery, chemotherapy and radiation dose escalation. Inclusion criteria were patients ≥ 65 years with a histologically confirmed ATC, staged according to the revised 8th edition of the Union for International Cancer Control Tumor–Node–Metastasis (UICC TNM) classification. The information was gained from pathological reports, which were available in all 26 cases. The study endpoints were the 6-, 12- and 24-month OS and PFS. Multimodal treatment was defined based on earlier reports such as trimodal therapy containing surgical resection and postoperative chemoradiotherapy (CRT) [22].

2.5. Criteria for Multimodal Treatment Approach

In accordance with the guidelines of the European Society for Medical Oncology (ESMO), surgical resection of the tumor burden (partial or total) was only performed in patients with a prospect of achieving R0/R1 status and was based on the perioperative risk assessment, as well as on comorbidities [11]. Importantly, M0 status was not an exclusion criterion for surgery. Similarly, radical CRT was performed subsequently if no absolute contraindications arose, such as a KPS status of <40% and/or poor liver or kidney function and cardiovascular comorbidities. Relative contraindications were discussed within multidisciplinary tumor boards consisting of surgeons, radiation oncologists and oncologists.

2.6. Statistical Analysis

Statistical analyses were performed using SPSS Statistics 25 (IBM, Chicago, IL, USA). Subgroups were compared by a log-rank test. All significant variables in the univariate analysis were included in a multivariate Cox regression analysis. The proportional hazard assumption of the Cox regression analysis was tested. PFS was defined as the time between the last day of radiotherapy and the occurrence of local or distant progression or death from all causes. OS was defined as the time between the last day of radiotherapy and death. For all statistical analyses, $p \leq 0.05$ was considered statistically significant.

3. Results

3.1. Systematic Review of Literature

Our search criteria with combinations of terms and operators are shown in Figure 1. In total, 162 publications were yielded using PubMed/MEDLINE databases. The Cochrane database did not provide any additional studies. Abstracts of these studies were screened for eligibility and excluded for the reasons shown in Figure 1. Ninety-eight potentially relevant publications underwent full-text assessment for eligibility and are included in Table 1. The matching criteria are shown in Figure 1. As a result, 43 publications were included in our systematic review of the literature with a total of 15 722 ATC patients diagnosed or analyzed in the past 20 years. In 33 (76.7%) of the included studies, younger age was significantly associated with a favorable outcome, at least in the univariate analysis. Furthermore, in 23 (53.5%) publications, age achieved significance in the multivariate analysis. Importantly, the most commonly chosen cut-off values for age were 70 (21%) and 65 (18.6%) years, representing cohorts of 2213 and 7923 patients, respectively. A review of the literature was undertaken by two authors (T.A. and D.O.) in order to minimize the risk of selection bias.

Table 1. Systematic review of the literature: age as a prognostic factor in patients with anaplastic thyroid cancer (ATC).

Author	Number of Patients (*N*)	Treatment	Age Cut-Off (Years)	Results
Sugitani et al. (2001) [23]	47	Multimodal—20% Other—80%	40–49 (7%) 50–59 (16%) 60–69 (34%) 70–79 (35%) 80–89 (7%)	Age was not a significant prognostic factor in the uni- or multivariate analysis
Pierie et al. (2002) [24]	67	Surgery—67% EBRT—84% ChT—31%	Cut-off: 70 ≤70 (45%) >70 (55%)	An age of ≤70 years was an independent predictor for beneficial OS (HR = 0.47, $p < 0.023$)
Kihara et al. (2004) [25]	19	Surgery—53% RT—68% ChT—63%	Cut-off: 70 40–49 (5%) 50–59 (0%) 60–69 (26%) 70–79 (32%) 80–89 (37%)	Age was not a significant prognostic factor in the uni- or multivariate analysis

Table 1. *Cont.*

Author	Number of Patients (*N*)	Treatment	Age Cut-Off (Years)	Results
Kebebew et al. (2005) [18]	516	Surgery—49% EBRT—63.2% ChT—not reported	Cut-off: 60 Mean: 71.3 (15–95)	An age of <60 years was an independent predictor for beneficial survival (HR = 0.482, 95% CI = 0.268–0.867, $p < 0.05$)
Brignardello et al. (2007) [26]	27	Surgery + adjuvant RT/ChT—56% Surgery + neoadjuvant RT/ChT—19% ChT alone—19% Unilateral palliative surgery—12%	Median: 70 (46–92)	Age was not a significant prognostic factor in the uni- or multivariate analysis
Kim et al. (2007) [27]	121	postoperative: 42.9% only RT, 7.1% only ChT and 14.3% both Bilateral curative surgery—59% postoperative: 50.7% only RT, 8.5% only ChT and 12.7% both RT alone—10.7% ChT alone—1.7% ChT/RT—4.1%	Cut-off: 60 <60 (33%) ≥60 (67%)	An age of <60 years was an independent predictor for lower disease-specific mortality(HR = 0.47, 95% CI = 0.30–0.74, $p = 0.001$)
Chen et al. (2008) [28]	261	Surgery only—26.1% EBRT alone—14.2% Surgery + EBRT—49.4%	<45 (5.7%) 45–54 (9.2%) 55–64 (19.9%) 65–74 (29.1%) 75–84 (23.4%) ≥85 (12.6%)	Younger age was an independent predictor for improved overall survival (HR = 1.02, 95% CI = 1.00–1.03, $p = 0.007$)
Yau et al. (2008) [29]	50	Surgery—68% EBRT—46% ChT—36%	Cut-off: 65 ≤65 (28%) >65 (72%)	In the univariate analysis, an age of ≤65 years was significantly associated with improved survival ($p = 0.025$) No significance in the multivariate analysis
Bhatia et al. (2009) [30]	53	Surgery—58.5% RT—100% CRT—73.6% Sequential ChT—16.9%	Median: 66.1 (27–88)	Age was not a significant prognostic factor in the uni- or multivariate analysis
Roche et al. (2010) [31]	26	Surgery—84.6% RT—53.8% ChT—19.2%	Mean: 75 (52.3–90.8)	Age >75 years was an independent predictor for poor prognosis ($p < 0.05$)
Akaishi et al. (2011) [32]	100	Surgery—70% RT—78% ChT—28%	Cut-off: 70 <70 (52%) ≥70 (48%)	Age ≥70 years was a significant risk factor for poorer survival in the multivariate analysis (RR = 1.03, 95% CI = 1.01–1.05, $p = 0.014$)
Derbel et al. (2011) [33]	44	Surgery alone—4.5% Surgery + CT—7% Surgery + RT + CT—79.5% RT alone—4.5% Surgery + RT—4.5%	Cut-off: 65 Median 65 (44–80)	An age of >65 years was associated with poorer outcome in the univariate analysis (HR = 2.36, 95% CI = 1.15–4.84, no *p*-value reported)
Sherman et al. (2011) [34]	37	Surgery + CRT—51% CRT—100%	Cut-off: 70 <70 (73%) ≥70 (27%)	An age of <70 years was an independent predictor for beneficial OS (HR = 0.32, 95% CI = 0.13–0.78, $p = 0.013$)
Tashima et al. (2011) [35]	33	Surgery—58% RT—52% ChT—39% RT + ChT—36%	Cut-off: 60 Median: 68 (26–93)	In the univariate analysis, an age of >60 years was associated with decreased survival ($p = 0.04$). No significance in the multivariate analysis
Sugitani et al. (2012) [36]	677	Surgery—45% EBRT—59% ChT—47%	Cut-off: 70 <70 (48%) ≥70 (52%)	An age of <70 years was an independent predictor for beneficial survival (HR = 1.28, 95% CI = 1.04–1.58, $p = 0.020$)
Haymart et al. (2013) [3]	2742	Surgery—50.2% RT—58.2% ChT—38.8%	≤44 (3.0%) 45–64 (27.5%) 65–74 (27.5%) 75–84 (30.4%) ≥85 (11.7%)	An age of ≥85 years was associated with greater mortality in the adjusted Cox regression model (HR = 3.43, 95% CI = 2.34–5.03, $p < 0.05$)
Dumke et al. (2014) [37]	40	Surgery—80% RT—98% ChT—15%	Median: 67 (38–84)	Age was not a significant prognostic factor in the uni- or multivariate analysis
Mohebati et al. (2014) [38]	83	Surgery alone—12% RT alone—4% ChT/RT—5% Surgery + RT + ChT—46%	Cut-off: 60 ≤60 (35%) >60 (65%)	1-year DSS ($p = 0.012$) in the univariate analysis ≤60 (52%) >60 (24%) No significance in the multivariate analysis
Polistena et al. (2014) [39]	79	Surgery—57% RT—59% ChT—100%	Cut-off: 75 <75 (53%) >75 (47%)	Patients <75 years and with tumors <5 cm in extent had the most favorable prognosis among subgroups in the univariate analysis ($p < 0.05$)
Sun et al. (2014) [12]	42	Surgery alone—29% EBRT alone—12% ChT alone—5% Surgery + RT—26% Surgery + RT/ChT—14% Surgery + ChT—10%	Cut-off: 55 <55 (33%) ≥55 (67%)	In the univariate analysis, an age of ≤55 years was significantly associated with improved 1- and 3-year overall survival rates ($p = 0.012$) No significance in the multivariate analysis
Ziveljevic et al. (2014) [17]	150	Surgery—57% Pre-OP RT—2.4% Post-OP RT—78.7% ChT—79%	≤50 (7.3%) 51–70 (73.3%) ≥70 (19.3%)	Younger age was an independent predictor of favorable survival (OR = 0.68, 95% CI = 0.49–0.95, $p = 0.023$)
Lo et al. (2015) [40]	15	Surgery—47% RT—20% ChT—0%	Median: 63 (36–73)	Age was not a significant prognostic factor in the uni- or multivariate analysis

Table 1. *Cont.*

Author	Number of Patients (*N*)	Treatment	Age Cut-Off (Years)	Results
Paunovic et al. (2015) [41]	150	Surgery—56.7% Pre-OP RT—2.4% Post-OP RT—78.8% ChT—2.4%	<40 (1.3%) 41–50 (6.1%) 51–60 (19.3%) 61–70 (54.0%) >70 (19.3%)	An age of <50 years is an independent predictor associated with overall survival (RR = 0.68, 95% CI = 0.49–0.95, $p = 0.023$)
Baek et al. (2016) [42]	329	RT/cCRT—15.2% Curative resection—28.6% Curative resection and adjuvant RT/cCRT—25.5% Curative resection and adjuvant ChT—3.0% ChT alone—3.0%	Cut-off: 70 <70 (51.7%) ≥70 (48.3%)	An age of ≥70 years was an independent predictor for poorer disease-specific survival (HR = 1.493, 95% CI = 1.134–1.965, $p < 0.01$)
Glaser et al. (2016) [43]	3552	Surgery—49.5% RT—58.7% ChT—41.6%	Cut-off: 65 <65 (31.6%) ≥65 (68.4%)	An age of <65 years was an independent predictor for improved overall survival (HR = 1.42, 95% CI = 1.26–1.60, $p < 0.0005$)
Käsmann et al. (2016) [44]	9	Surgery—78% RT—78% ChT—78%	Cut-off: 64 ≤64 (56%) >64 (44%)	Age was not a significant prognostic factor in the uni- or multivariate analysis
Lee et al. (2016) [13]	98 (ATC)	Surgery-based—58.2% EBRT-based—17.3% ChT—7.1%	Mean: 63.4 ± 13.4	Age at diagnosis in years achieved significance in the multivariate analysis (OR = 1.022, 95% CI = 0.01–1.10, $p = 0.029$) in a group, where resectability was adjusted with age, tumor size, WBC count and N status
Lennon et al. (2016) [45]	64	Surgery alone—17.2% RT alone—26.6% ChT alone—4.7% Surgery + RT—10.9% RT + ChT—9.4% Surgery + RT + ChT—12.5%	Cut-off: 70 Median: 72 (47–93)	In the univariate analysis, an age of >70 years was associated with improved overall survival ($p = 0.041$) No significance in the multivariate analysis
Liu et al. (2016) [6]	50	Total or extensive thyroidectomy—76% Palliative resection of cervical lymph nodes—6% RT—32% ChT—16%	Cut-off: 60 ≤60 (52%) >60 (48%)	Age was not a significant prognostic factor in the uni- or multivariate analysis
Pezzi et al. (2016) [5]	1288	Surgery (any neck, but only R2)—11.6% RT—47.7% ChT—53.8%	Cut-off: 65 Average: 70.4	An age of <65 years was an independent predictor for beneficial patient survival (HR = 1.317, 95% CI = 1.137–1.526, $p < 0.001$)
Wendler et al. (2016) [16]	100	Surgery—83% EBRT—81% ChT—56%	Cut-off: 70 <70 (46%) ≥70 (54%)	An age of <70 years was an independent predictor for beneficial survival (HR = 1.048, 95% CI = 1.015–1.082, $p = 0.004$)
Hvilsom et al. (2017) [46]	219	Thyroid surgery (R0—2)—50.7% Lymph node surgery—72% ChT/RT—Not reported	Median: 74 (30–94)	An age of ≤73.6 years was an independent predictor for improved overall survival (HR = 1.4, 95% CI = 1.0–2.0)
Jacobsen et al. (2017) [47]	31	Surgery—42% RT—100% ChT—74%	Median: 69 (26–87)	In the univariate analysis, age at diagnosis in years achieved significance (HR = 1.02, 95% CI = 0.98–1.07) No significance in the multivariate analysis
Park et al. (2018) [48]	41	Surgery + RT + ChT—39% Surgery + RT—12.2% RT + ChT—36.6% RT alone—12.2%	Cut-off: 65 <65 (31.7%) ≥65 (68.3%)	Age was not associated with better/poorer outcome in the univariate analysis (HR = 1.44, 95% CI = 0.69–3.01, $p = 0.328$)
Takahashi et al. (2018) [49]	33	Surgery—39% ChT—52% CRT—45%	Median 68 (41–87)	Age (≥ median vs. < median) was not associated with better/poorer outcome in the univariate analysis (HR= 1.22, 95% CI = 0.57–2.60, $p = 0.605$)
Corrigan et al. (2019) [15]	28	Surgery—71.4% EBRT—75% ChT—50%	Not reported	Younger age is an independent predictor for better overall survival (HR = 1.079; 95% CI = 1.022–1.139; $p = 0.006$)
Fan et al. (2019) [22]	104	ChT/RT—95.2% Surgery + RT + ChT—51%	Cut-off: 70 Median: 63.5 (28–87)	In the univariate analysis, the age of <70 years was significantly associated with improved overall survival ($p = < 0.001$) No significance in the multivariate analysis
Huang et al. (2019) [50]	735	Surgery—26% RT—36% ChT—31% No treatment—22%	Cut-off: 70 Median: 70 IQR: 60–80	Age at diagnosis in years achieved significance in the multivariate analysis (HR = 1.022, 95% CI = 1.010–1.034, $p < 0.001$) No difference in favor for the subgroups ≤/>70 years in terms of total thyroidectomy
Li et al. (2019) [51]	1048	Primary surgery—45% EBRT—55% ChT—42%	Cut-off: 65 <65 (33%) ≥65 (67%)	An age of ≥65 years was an independent predictor for overall survival (HR = 1.34, 95% CI = 1.16–1.55, $p < 0.001$)
De Ridder et al. (2020) [52]	812	Surgery—12% Surgery + RT—15% Surgery + cCRT—2% Surgery + RT + ChT—3% Surgery + ChT—1% RT—28% cCRT—1% RT + ChT—3% ChT—1%	Median: 73 (29–99)	Age at diagnosis was an independent prognostic factor for poorer outcome (HR = 1.014, 95% CI = 1.006–1.020, $p < 0.001$)
Gui et al. (2020) [53]	1404	Surgery—44% EBRT—59% ChT—not reported	Cut-off: 65 <65 (34%) ≥65 (66%)	An age of ≥65 years was an independent predictor for worse overall survival (HR = 1.525, 95% CI = 1.326–1.752, $p < 0.001$)

Table 1. *Cont.*

Author	Number of Patients (*N*)	Treatment	Age Cut-Off (Years)	Results
Lin et al. (2020) [54]	1567/717	Surgery—566/1567 (36%) Not reported for RT/ChT	Median: 71 (23–100)	Younger age is an independent predictor for overall survival (HR = 1.02, 95% CI = 1.01–1.02, $p < 0.001$)
Saeed et al. (2020) [55]	496	Surgery—100% Adjuvant EBRT—76% Adjuvant Chemotherapy—59% Adjuvant CRT—56.4%	Cut-off: 65 <65 (42%) ≥65 (58%)	In the univariate analysis, an age of ≥65 years was a significant prognostic factor for overall survival ($p = 0.04$) No significance in the multivariate analysis

External Beam Radiation Therapy (EBRT), Chemotherapy (ChT), Overall Survival (OS), Hazard Ratio (HR), Odds Ratio (OR), Relative Risk (RR), Radiation Therapy (RT), Confidence Interval (CI), Chemoradiotherapy (CRT), concurrent chemoradiotherapy (cCRT), Disease Specific Survival (DSS).

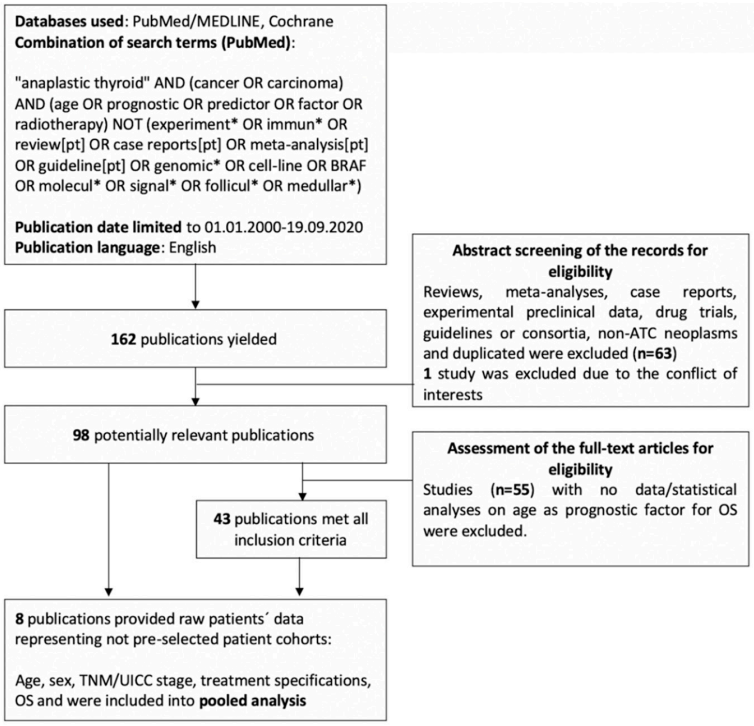


Figure 1. PRISMA flowchart for the systematic review.

3.2. Results of the Pooled Analysis

The individual patient data of eight eligible publications were extracted ($n = 186$) (Table 2) [49,56–62]. The median age at initial diagnosis was 68 (range = 35–92) years. Treatment consisted of surgery in 95 (51%), radiotherapy in 152 (82%) and sequential or concurrent chemotherapy in 114 (61%) of all patients. Multimodal treatment containing surgery followed by postoperative chemoradiotherapy was administered in 74 (40%) patients. Fifty-one (27%) patients were diagnosed with metastatic disease (UICC stage IVC).

The median OS was 5.9 months (range: 0–157). Survival rates at 6, 12 and 24 months were 50%, 24% and 15%, respectively. Surgery ($p < 0.001$), radiotherapy ($p < 0.001$), sequential or concurrent chemotherapy ($p < 0.001$) and administering multimodal treatment ($p < 0.001$) were prognostic factors concerning OS in the univariate analysis. In the multivariate analysis, radiotherapy ($p < 0.001$, hazard ratio (HR) = 0.383, 95% confidence interval (CI) = 0.253–0.579) was significantly associated with an improved OS, whereas surgery ($p = 0.107$, HR = 0.640, 95% CI = 0.372–1.100), sequential or concurrent chemotherapy ($p = 0.067$, HR = 0.664, 95% CI = 0.428–1.029) and multimodal treatment ($p = 0.464$, HR = 0.777, 95% CI = 0.396–1.526) did not achieve significance in the multivariate analysis.

Table 2. Patient and treatment characteristics of the pooled patient cohort.

Parameter	Value (%)
Total	186 (100)
Age, years (range)	68 (35–92)
Gender	
Male	54 (39)
Female	60 (44)
Unknown	24 (17)
UICC stage	
IVA/B	113 (61)
IVC	51 (27)
Unknown	22 (12)
Surgery	
No	91 (49)
Yes	95 (51)
Radiotherapy	
No	34 (18)
Yes	152 (82)
Sequential or concurrent chemotherapy	
No	72 (39)
Yes	114 (61)
Multimodal treatment	
No	112 (60)
Yes	74 (40)

Union of International Cancer Control (UICC).

3.3. Propensity Score Matching (PSM)

Individual patients' data of all eligible patient cohorts [49,56–62] were included according to our database assessment protocol in the propensity score matching (PSM) analysis. Patients aged <64 years were matched in a 1:1 ratio to patients aged ≥65 years. To each patient aged <64 years, one corresponding patient aged ≥65 years with exactly the same UICC stage (IVA/B vs. IVC) was matched. PSM also considered the treatment mode, including surgery and chemotherapy. Sixty-nine patients aged <64 years were matched to 69 patients aged ≥65 years (Table 3). Surgery ($p < 0.001$), radiotherapy ($p < 0.001$), concurrent or sequential chemotherapy ($p < 0.001$) and younger age ($p = 0.005$) were associated with an improved OS in the univariate analysis (Figure 2), whereas gender did not achieve significance ($p = 0.96$). In the multivariate analysis, surgery ($p < 0.001$, HR = 0.294, 95% CI = 0.192–0.45), radiotherapy ($p < 0.001$, HR = 0.042, 95% CI = 0.018–0.098) and younger age ($p = 0.008$, HR = 1.721, 95% CI = 1.151–2.573) were significantly associated with an improved OS, whereas concurrent or sequential chemotherapy ($p = 0.171$, HR = 1.406, 95% CI = 0.863–2.289) failed to achieve significance.

Table 3. Patient and treatment characteristics of the propensity score cohort.

Parameter	Entire PSM Cohort, *N* (%)	Subgroup with Patients Aged < 65 Years, *N* (%)	Subgroup with Patients Aged ≥ 65 Years, *N* (%)	*p*-Value
Total	138 (100)	69 (50)	69 (50)	
Age, years (range)	65 (35–92)	56 (35–64)	74 (65–92)	<0.001
Gender				
Male	54 (39)	33 (48)	21 (30)	
Female	60 (44)	22 (32)	38 (55)	0.009
Unknown	24 (17)	14 (20)	10 (15)	
UICC stage				
IVA/B	92 (67)	46 (67)	46 (67)	0.999
IVC	46 (33)	23 (33)	23 (33)	
Surgery				
No	59 (43)	27 (39)	32 (46)	0.391
Yes	79 (57)	42 (61)	37 (54)	
Radiotherapy				
No	14 (10)	8 (12)	6 (9)	0.574
Yes	124 (90)	61 (88)	63 (91)	
Sequential or concurrent chemotherapy				
No	54 (39)	18 (26)	36 (52)	0.002
Yes	84 (61)	51 (74)	33 (48)	

Union for International Cancer Control (UICC).

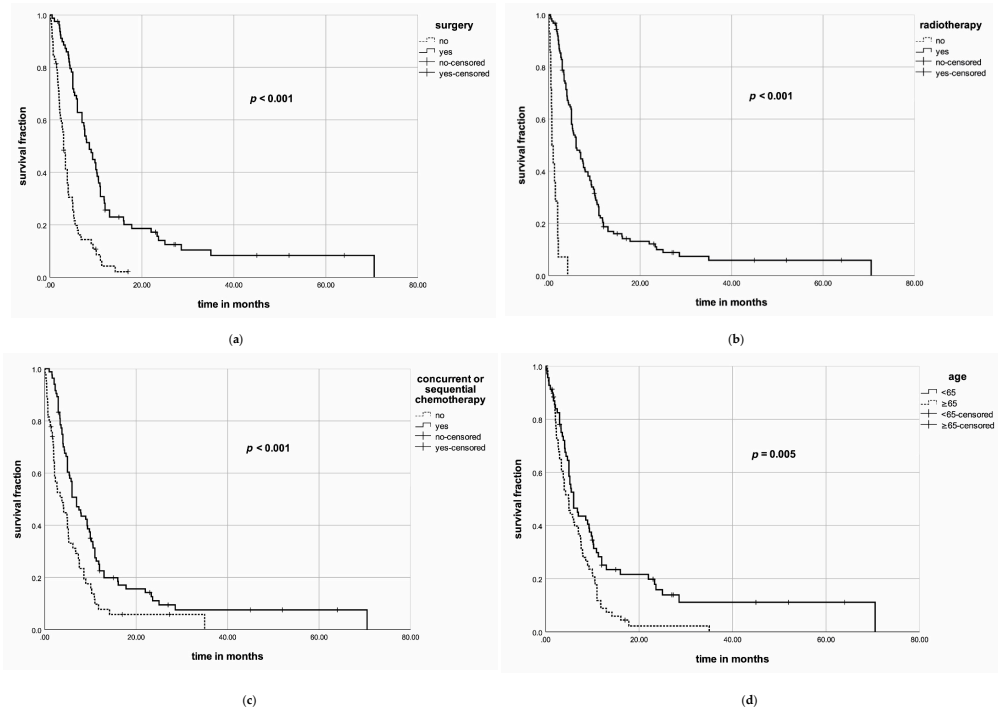


Figure 2. (**a**). Kaplan–Meier curve for surgery and overall survival in the univariate propensity score matching (PSM) analysis; (**b**) Kaplan–Meier curve for radiotherapy and overall survival in the univariate PSM analysis; (**c**) Kaplan–Meier curve for sequential or concurrent chemotherapy and overall survival in the univariate PSM analysis; (**d**) Kaplan–Meier curve for age and overall survival in the univariate PSM analysis.

3.4. Patient Characteristics of Our Single-Center Cohort

The median age at initial diagnosis was 74 (65–97) years and 13 (50%) of all patients were female. The Karnofsky performance status (KPS) was ≤70% in 12 (46%) and >70% in 14 patients (54%). In only one (4%) patient, the disease was limited to the thyroid gland (stage IVA). Nine (35%) patients had extrathyroidal infiltrations (stage IVB) and 16 (62%) already showed distant metastases (stage IVC), respectively (Table 4). At initial diagnosis, 62% of patients had distant metastases that were found in one (44%), two (44%), three (6%) or four (6%) different organs. Ninety-four percent of the metastases were localized pulmonary, 50% lymphatic, 19% osseous, 6% hepatic and 6% cerebral (Table 2). Twelve patients (46%) were treated in a multimodal approach (Table 5 + CRT cohort).

Table 4. Eighth edition of the Union for International Cancer Control Tumor–Node–Metastasis (UICC TNM) classification.

Stage	Eighth Edition of UICC TNM
IVA	T1–3a, N0 and M0 T1: Tumor ≤ 2 cm in the greatest dimension limited to the thyroid T2: Tumor > 2 cm but ≤4 cm in the greatest dimension limited to the thyroid T3a: Tumor > 4 cm limited to the thyroid
IVB	T1–3a, N1 and M0 or T3b–T4b, any N and M0 T3b: Gross extrathyroidal extension invading only strap muscles (sternohyoid, sternothyroid, thyrohyoid and omohyoid muscles) from a tumor of any size T4a: Gross extrathyroidal extension invading subcutaneous soft tissues, larynx, trachea, esophagus or recurrent laryngeal nerve from a tumor of any size T4b: Gross extrathyroidal extension invading prevertebral fascia or encasing a carotid artery or mediastinal vessels from a tumor of any size
IVC	Any T, any N and M1

Union of International Cancer Control (UICC), Tumor (T), Node (N), Metastases (M).

Table 5. Patient- and treatment-related characteristics.

Parameter	*n*
Age, years	
<74	11 (42%)
≥74	15 (58%)
Gender	
Male	13 (50%)
Female	13 (50%)
KPS, %	
≤70	12 (46%)
>70	14 (54%)
T stage	
2–3	2 (8%)
4	24 (92%)
N stage	
0	10 (39%)
1	16 (62%)
M stage	
0	10 (39%)
1	16 (62%)
Number of metastatic sites	
1	7 (44%)
2	7 (44%)
3	1 (6%)
4	1 (6%)
UICC stage	
IVA	1 (4%)
IVB	9 (35%)
IVC	16 (62%)
Surgery	
No	14 (54%)
Yes	12 (46%)
Chemotherapy	
No	13 (50%)
Yes	13 (50%)
Treatment	
RT/CRT	14 (54%)
S+CRT	12 (46%)
Resection status	
R0	1 (8%)
R1	7 (58%)
R2	4 (33%)
EQD2 level	
≤49	14 (54%)
>49	12 (46%)
RT technique	
3D-CRT	17 (65%)
IMRT	9 (35%)

Karnofsky performance status (KPS), Tumor (T), Node (N), Metastases (M), Union of International Cancer Control (UICC), Radiation Therapy (RT), Chemoradiotherapy (CRT), three-dimensional conformal radiotherapy (3D-CRT), equivalent dose in 2 Gy fractions (EQD2), intensity-modulated radiation therapy (IMRT).

3.5. Treatment-Related Characteristics

A hemithyroidectomy was performed in four (15%) patients, total and subtotal thyroidectomy in six (23%) and two (8%) patients, respectively. Chemotherapy was administered in 13 (50%) patients. Of those, six (46%) patients received concurrent chemotherapy with carboplatin (area under the curve (AUC) = 2) and administered 50 mg/m^2 paclitaxel weekly. Single-agent chemotherapy with doxorubicin (10 or 20 mg/m^2) was given weekly concurrent to radiation in five (38%) patients. Sequential chemotherapy was given in two (15%) patients (paclitaxel with carboplatin or pemetrexed). Irradiation was administered using a three-dimensional conformal radiotherapy (3D-CRT) technique in 17 (65%) patients. Nine (35%) patients were treated using intensity-modulated radiation therapy (IMRT) (Table 5). The cumulative radiation dose was calculated in equivalent dose in 2 Gy fractions (EQD2). The median EQD2 was 49 Gy (range = 5–71).

3.6. Treatment-Related Toxicities

Treatment-emerged adverse events (TEAE) were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4. The most common side effects were dysphagia, dermatitis, mucositis, dyspnea and dysphonia. Acute grade 3 toxicity of dysphagia, dyspnea, dermatitis, mucositis and dysphonia was found in 23%, 15%, 12%, 12% and 8% of patients. Therapy-related toxicity grade 4/5 was not observed. An EQD2 of ≥40 Gy was associated with radiation-induced dermatitis grade ≥ 2 ($p = 0.04$), as well as with dysphagia grade ≥ 2 ($p = 0.005$) and mucositis grade ≥ 2 ($p = 0.04$). Dyspnea grade ≥ 2 was not correlated with an EQD2 of ≥40 Gy ($p = 0.07$).

3.7. Outcomes on Survival and Relapse in the Single-Center Evaluation

The median OS after the end of radiotherapy was three months (range = 0–125, 95% confidence interval (CI) = 0.75–5.29). The 6-, 12- and 24-month survival rates were 35%, 22% and 11%, respectively. The median PFS after the end of radiotherapy was two months (range = 0–125, 95% CI = 0.34–3.66). Local recurrence was observed in three (12%) patients during follow-up.

3.8. Patient- and Treatment-Related Factors of Prognosis in the Single-Center Evaluation

In the univariate analyses, KPS (>70%), N category, M category, UICC stage, surgery, multimodal treatment and an EQD2 of >49Gy were associated with an improved OS (Figure 3). In the multivariate analysis, for OS, none of the following factors achieved significance: KPS (hazard ratio (HR) = 0.42, 95% confidence interval (95% CI) = 0.07–2.64, $p = 0.36$), UICC stage (HR = 1.45, 95% CI = 0.34–6.22, $p = 0.62$), multimodal therapy (HR = 0.52, 95% CI = 0.07–3.91, $p = 0.52$) or EQD2 level (HR = 0.56, 95% CI = 0.14–2.32, $p = 0.43$) (Table 6). Univariate analysis of PFS, KPS (>70%), N category, M category, surgery, multimodal therapy and an EQD2 > 49 Gy resulted in improved PFS (Figure 4a–e). In the multivariate analysis, none of the following factors had a significant impact on PFS (Table 7): KPS (HR = 1.63, 95% CI = 0.35–7.45, $p = 0.53$), N category (HR = 1.81, 95% CI = 0.56–5.92, $p = 0.33$), M category (HR = 1.94, 95% CI = 0.45–8.32, $p = 0.37$), multimodal therapy (HR = 0.41, 95% CI = 0.06–2.72, $p = 0.35$) or EQD2 level (HR = 0.95, 95% CI = 0.21–4.34, $p = 0.94$).

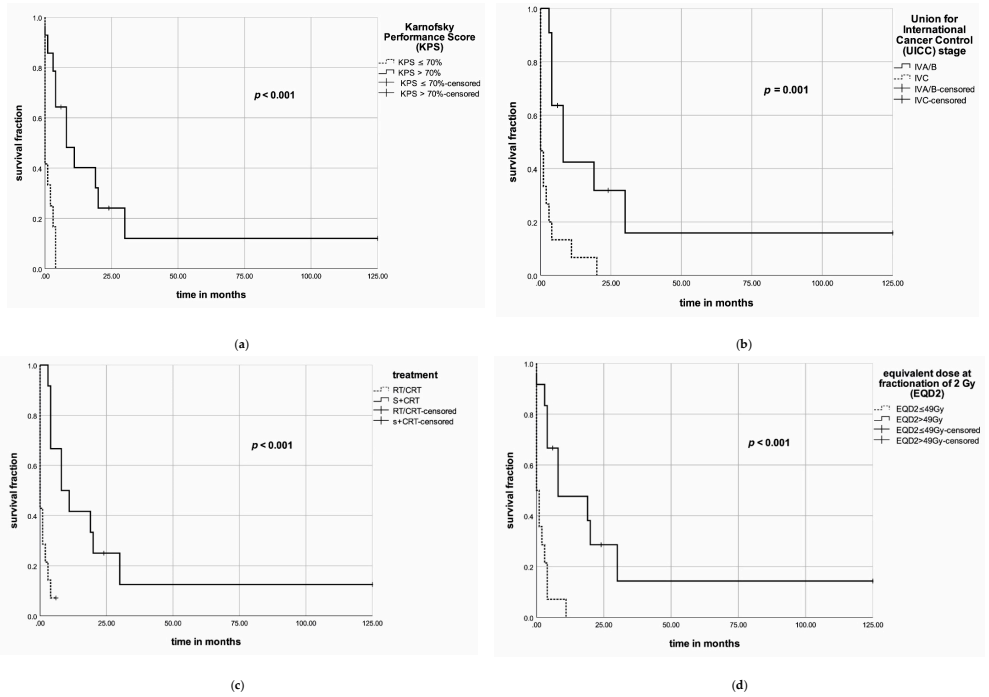


Figure 3. (**a**) Kaplan–Meier diagram for the Karnofsky performance status (KPS) and overall survival; (**b**) Kaplan–Meier diagram for the UICC stage and overall survival; (**c**) Kaplan–Meier diagram for treatment approaches and overall survival; (**d**) Kaplan–Meier diagram for EDQ2 levels and overall survival.

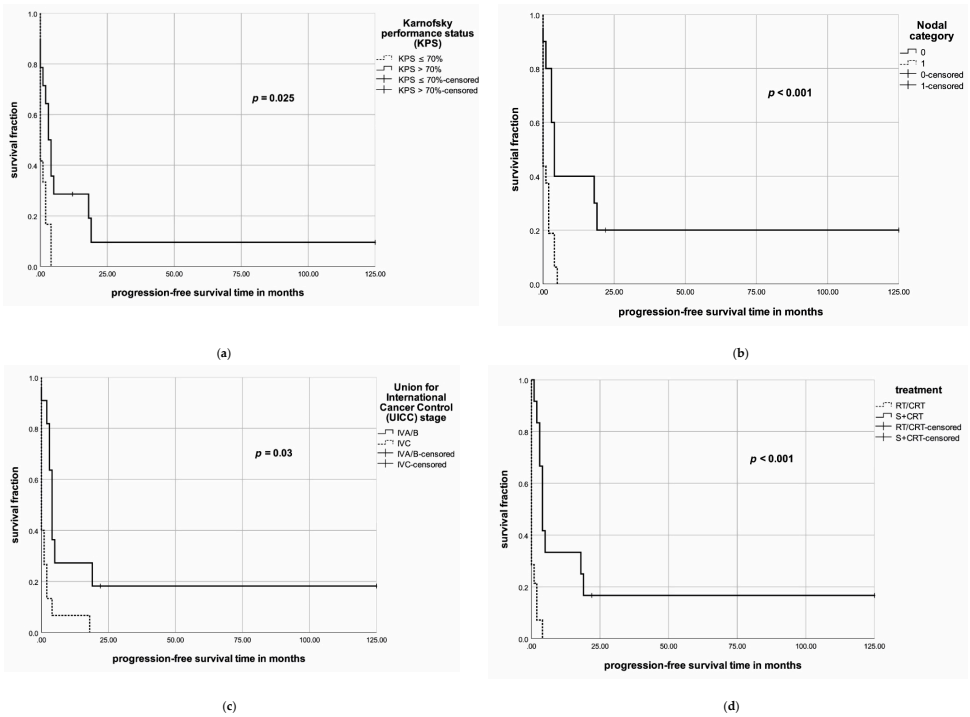
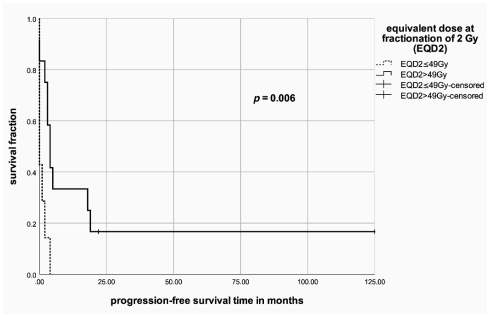


Figure 4. *Cont.*



(e)

Figure 4. (**a**) Kaplan–Meier diagram for the KPS and progression-free survival (PFS); (**b**) Kaplan–Meier diagram for N status and PFS; (**c**) Kaplan–Meier diagram for the UICC stage and PFS; (**d**) Kaplan–Meier diagram for treatment approaches and PFS; (**e**) Kaplan–Meier diagram for EDQ2 levels and PFS.

Table 6. Uni- and multivariate analysis of overall survival (OS).

	Univariate Analysis				Multivariate Analysis			
Parameter	**At 6 Months**	**At 12 Months**	**At 24 Months**	***p*-Value**	***p*-Value**	**Hazard Ratio**	**95% CI Lower**	**95% CI Upper**
Age, years								
≤74	55%	36%	12%	0.15	-	-	-	-
>74	22%	10%	10%					
Gender								
Male	23%	23%	12%	0.45	-	-	-	-
Female	46%	19%	9%					
KPS, %								
≤70	0%	0%	0%	<0.001	0.357	0.422	0.068	2.64
>70	64%	40%	20%					
N stage								
0	50%	40%	27%	0.028	-	-	-	-
1	25%	8%	0%					
M stage								
0	70%	47%	31%	0.001	-	-	-	-
1	13%	6%	0%					
UICC stage								
IVA	100%	100%	100%	0.004	0.618	1.449	0.337	6.223
IVB	67%	40%	27%					
IVC	13%	6%	0%					
Surgery								
No	7%	0%	0%	<0.001	-	-	-	-
Yes	67%	42%	21%					
Chemotherapy								
No	31%	21%	21%	0.78	-	-	-	-
Yes	39%	23%	0%					
Treatment								
RT/CRT	7%	0%	0%	<0.001	0.524	0.519	0.069	3.911
S+CRT	67%	42%	21%					
EQD2 level								
≤49	7%	0%	0%	<0.001	0.426	0.562	0.136	2.32
>49	67%	42%	24%					
RT technique								
3D-CRT	29%	12%	6%	0.18	-	-	-	-
IMRT	44%	44%	22%					

Karnofsky performance status (KPS), Node (N), Metastases (M), Union of International Cancer Control (UICC), Radiation Therapy (RT), Chemoradiotherapy (CRT), three-dimensional conformal radiotherapy (3D-CRT), equivalent dose in 2 Gy fractions (EQD2), intensity-modulated radiation therapy (IMRT).

Table 7. Uni- and multivariate analysis of progression-free survival (PFS).

	Univariate Analysis				Multivariate Analysis			
Parameter	**At 3 Months**	**At 6 Months**	**At 12 Months**	***p*-Value**	***p*-Value**	**Hazard Ratio**	**95% CI Lower**	**95% CI Upper**
Age, years								
≤74	27%	27%	27%	0.29	-	-	-	-
>74	27%	7%	7%					
Gender								
Male	31%	23%	23%	0.82	-	-	-	-
Female	23%	8%	8%					
KPS, %								
≤70	17%	0%	0%	0.025	0.532	1.625	0.354	7.452
>70	36%	29%	29%					
N stage								
0	60%	40%	40%	<0.001	0.325	1.812	0.555	5.919
1	6%	0%	0%					
M stage								
0	40%	30%	30%	0.03	0.373	1.939	0.452	8.318
1	19%	6%	6%					
UICC stage								
IVA	100%	100%	100%	0.056	-	-	-	-
IVB	33%	22%	22%					
IVC	19%	6%	6%					
Surgery								
No	7%	0%	0%	<0.001	-	-	-	-
Yes	50%	33%	33%					
Chemotherapy								
No	15%	15%	15%	0.36	-	-	-	-
Yes	39%	15%	15%					
Treatment								
RT/CRT	7%	0%	0%	<0.001	0.352	0.405	0.06	2.718
S+CRT	50%	33%	33%					
EQD2 level								
≤49	14%	0%	0%	0.006	0.944	0.947	0.207	4.34
>49	42%	33%	33%					
RT technique								
3D-CRT	18%	6%	6%	0.18	-	-	-	-
IMRT	44%	33%	33%					

Karnofsky performance status (KPS), Tumor (T), Node (N), Metastases (M), Union of International Cancer Control (UICC), Radiation Therapy (RT), Chemoradiotherapy (CRT), three-dimensional conformal radiotherapy (3D-CRT), equivalent dose in 2 Gy fractions (EQD2), intensity-modulated radiation therapy (IMRT).

4. Discussion

The main goal of this report was to investigate the prognostic impact of age in the treatment of ATC, as well as to study real-world clinical data and outcomes from elderly patients with ATC who received multimodal therapy outside the framework of a clinical trial. To our knowledge, this is the first comprehensive experience reported to date, evaluating patients aged ≥65 years in order to investigate the outcomes concerning OS and PFS, treatment-related toxicity and prognostic factors.

In general, age appears to be an important risk factor for the outcomes in patients with ATC [3,4,12,15–18]. Two multicenter studies with almost 3000 patients found increasing age as a prognostic factor, resulting in a less favorable outcome [3,17]. In the study of Wendler et al. with 100 patients, an age > 70 was found to be an independent prognostic factor for shorter OS [16]. This is in accordance with a large registry study from Japan that included 677 ATC patients [4]. They also found an age > 70 associated with a decreased OS, while an analysis of Surveillance, Epidemiology and End Results Program (SEER) data with 516 patients reports that patients older than 60 years already suffer from higher mortality rates [18]. Their data show a difference of 28% in cancer-specific survival (CSS) after a follow-up of one year when comparing patients over 60 with those under 60 years of age. On the other hand, the single-center cohort with 54 patients from Rao et al. found no association of patients above 60 years with worse OS ($p = 0.5$). This might be due to the small cohort and a relatively low median age of 63 years [14].

Wendler et al. confirmed that age has a severe impact on treatment allocation. In patients <60 years, 77% received multimodal therapy, while in the group >80 years only 17% received this aggressive treatment approach [16]. Unfortunately, no reasons are given here for the individual assignments of therapies or conclusions regarding quality of life.

Based on the results of our systematic review and pooled analysis, age appears to have a prognostic impact on the outcome concerning OS. Elderly patients (aged ≥65 years) showed a significant association with poorer OS compared to younger patients. Therefore, elderly patients need to be considered as a special patient group in ATC treatment.

The KPS represents an important prognostic factor for OS and PFS in several types of cancer [20,63–65]. In our cohort, all patients with a KPS ≤ 70% died in less than six months. On the other hand, for patients with a KPS > 70%, the 6-, 12- and 24-month survival rates were 64%, 40% and even 20%, respectively. In ATC, KPS, as well as the Eastern Cooperative Oncology Group Performance Index (ECOG), are not frequently reported in the literature and their prognostic value remains controversial. Future studies need to address this issue and provide a performance status, e.g., ECOG or KPS, in order to consequently prevent selection bias.

Nodal involvement and distant metastases determine the UICC stage and are, therefore, important for clinical outcomes. According to Wendler et al. and Glaser et al. [16,43], nodal involvement impacts OS negatively. Additionally, many larger and smaller studies report that patients with distant metastases experience a dismal prognosis [4–6,12,16,43,50]. In our study cohort, local nodal involvement and distant metastases were associated with poor outcome, which corresponds with the published literature. We found a six-month overall survival rate of patients with nodal involvement at an initial diagnosis of 25%, while it was 50% for those who did not have nodal involvement at that time.

The UICC stage represents a clinically important prognostic factor for OS. In our study, patients were diagnosed according to the revised eighth edition of the UICC TNM classification. We found that OS, as well as PFS, strongly depend on the stage. The 6- and 12-month survival rates were as follows: 100% each in IVA stage; 67% and 40%, respectively, for stage IVB; and 13% and 6%, respectively, for stage IVC. Similarly, the results from the studies by Haymart et al. and Wendler et al. are consistent with our findings [3,16].

Importantly, more than 40% of all ATC cases occur in advanced stages, which means that symptoms of local compression with dyspnea and dysphagia and/or distant metastases are present [1,5,8,13,14,66]. These cases correspond to the unresectable stage IVB or stage IVC, in which, usually, no surgery or only an incomplete resection (R2) is possible [2,5,7]. In this situation, definitive chemoradiotherapy may provide local control and symptomatic relief [6–8,50].

According to the published literature, the administered radiation dose depends on treatment goals (palliative vs. curative treatment) and ranges mainly between 20 and 75 Gy [5,11]. Nevertheless, the exact radiation dose in curative settings remains highly controversial. We found a radiation dose of >49 Gy as a significant prognostic factor for OS and PFS, while other researchers described a dose of >60 Gy [5,22]. According to Fan et al., radiation doses of >60 Gy are associated with an improved local disease control ($p < 0.001$) and overall survival ($p = 0.004$). Differences were also found in the median OS for patients with radiotherapy (RT) doses of >60 Gy (10.6 months) vs. doses <60 Gy (3.6 months) [22]. Furthermore, the results of Glaser et al. show a more favorable outcome with higher-dose radiation (≥59.4 Gy) [43].

In accordance with the recent analysis of 1288 patients from the National Cancer Database (NCDB), radiotherapy can stop or delay the local growth process. As a result, patients with advancedstage IVB and IVC and unresectable tumors may benefit from more aggressive treatments. They found that patients who received radiation from 60 to 75 Gy had significantly better OS rates compared to patients with radiation doses from 45 to 59.9 Gy [5]. Our study found that a radiation dose of >49 Gy results in a more favorable OS, in addition to patients aged ≥65 years [6,11,12,16]. On the other hand, we found that an EQD2 of ≥40 Gy is associated with radiation dermatitis grade ≥2 ($p = 0.04$), as well as with dysphagia grade ≥2 ($p = 0.005$) and mucositis grade ≥2 ($p = 0.04$). Interestingly, dyspnea ($p = 0.07$) was

not associated with an irradiation dose. According to Fan et al., irradiation with >60 Gy in patients resulted in no grade 4 subacute or later adverse effects. However, common acute grade 3 adverse events were reported for dermatitis (20%), mucositis (13%), dysphagia (8%) and fatigue (7%) [22]. Similarly, to the results of Fan et al., no treatment-related toxicity grade 4/5 was observed in our study cohort. In contrast, our study cohort showed acute grade 3 toxicity of dermatitis and mucositis both only in 12% of all patients, which might be due to lower radiation doses. Severe dysphagia, however, was present in 23% of our patients. The reasons and possible confounders for this relatively high percentage are potentially due to the close surveillance of our patients and the proactive insertion of a percutaneous endoscopic gastrostomy (PEG) at our center.

The implementation of new radiation delivery techniques such as Intensity-Modulated Radiotherapy (IMRT) achieved improved outcomes concerning OS and PFS with less toxicity compared to older radiation techniques like 2D/3D-CRT [48]. The study by Park et al., which included 41 patients, found that IMRT (n = 28) resulted in a more favorable OS (HR = 0.40, p = 0.005) and PFS (HR = 0.33, p = 0.005) compared to 3D-CRT (n = 13). In addition, higher radiation doses could be safely achieved using IMRT rather than 3D-CRT (median doses of 66 Gy vs. 60 Gy, p = 0.005) [48]. A small cohort study by He et al. confirmed that with IMRT, the dose tolerance was significantly improved; almost all patients received higher-dose radiation (>54 Gy) [67]. On the other hand, Corrigan et al. emphasized the recommendation of IMRT in the treatment of neck and head cancer, but little evidence was available regarding the treatment of ATC. However, they also found an association between IMRT and higher 12-month survival rates compared to 2/3D-CRT [15]. In our study, we found a benefit for IMRT at the 12-month survival rate compared to 3D-CRT (44% vs. 12% at 12 months). However, the difference was not significant.

The administration of chemotherapy in our cohort resulted in no further improvement of OS and PFS. Several studies confirm our controversial findings [12,15,50]. In contrast, two German studies found a survival benefit for administering concurrent or sequential chemotherapy to radiotherapy [16,44]. However, administering concurrent chemotherapy to radiotherapy in ATC remains highly controversial especially in elderly patients. Tiedje et al. recently summarized the latest evidence and confirmed that it is still unclear whether chemotherapy or chemoradiotherapy may improve patients' outcomes. Moreover, administering chemotherapy only in stage IVC or also in stage IVA or IVB remains arguable [68].

Recent studies show that trimodal treatment (surgery, radiotherapy and chemotherapy) combined as a multimodal therapy significantly improves both OS and PFS in patients with ATC [3,5,11,13–16]. As a result, this multimodal therapy regime is increasingly becoming the standard of care, especially for patients in stage IVA and resectable stage IVB [1,12,14] and was incorporated into national and international guideline recommendations [1,69].

We found that elderly patients (≥65 years) appear to benefit from multimodal treatment including surgical resection followed by CRT compared to definitive chemo-/radiotherapy alone. Nonetheless, it failed to achieve significance in the multivariate analysis given the limitations of our study, such as limited patient number and the retrospective study design. The combination of surgery and chemoradiotherapy showed 6-, 12- and 24-month OS rates of 67%, 42% and 21%, respectively, compared to definitive chemo-/radiotherapy with 7%, 0% and 0%. Significantly improved PFS rates were also observed in 50%, 33% and 33% of patients compared to those with only definitive chemo-/radiotherapy of, again, 7%, 0% and 0%. Fan et al. observed in a cohort of 104 patients a 12-month OS rate of 54.7% in 53 patients who were treated with multimodal therapy. On the other hand, the 12-month overall survival rate in the 51 patients who were treated with concurrent chemoradiation or radiotherapy alone was only 12.8%. In the multivariate analysis, they also found multimodal treatment associated with improved local progression-free survival (LPFS) (p = 0.017). The 12-month LPFS rate in patients who were treated multimodally was 85.9% vs. 54.1% in those patients who were not (p = 0.003) [22]. Importantly, not all patients may tolerate combined or multimodal treatment approaches. Elderly patients with ATC need more attention and personalized treatment. In order

to optimize such personalized approaches, the patients' survival prognoses must be considered for decision-making. Therefore, our study revealed several prognostic factors, namely KPS, UICC, multimodal treatment and radiation dose escalation as well as outcome and toxicity in elderly patients.

Several limitations must be considered interpreting the results of the present study such as the retrospective nature and, therefore, a risk of including hidden selection and confounding biases. In addition, the patient cohort is relatively small with a long recruitment period.

According to our findings, treatment-related toxicity appears to be manageable in patients aged ≥65 years. Outcomes in elderly patients can be improved by more intensive therapy regimes such as combined treatments or dose escalation. We state that age does not need to be an exclusion factor for multimodal treatments and should be discussed within multidisciplinary tumor boards consisting of surgeons, oncologists and radiation oncologists.

5. Conclusions

Age is an independent prognostic factor in the treatment of ATC. Multimodal treatment including surgery and chemoradiotherapy in elderly patients with ATC appears to be associated with promising outcomes with manageable toxicity. Several prognostic factors for elderly patients were identified and may help physicians to estimate a patient's prognosis and tailoring personalized treatment approaches. Despite the rare occurrence, ATC remains highly lethal, and therefore, prospective studies in elderly patients are needed in order to improve future outcomes.

Author Contributions: Conceptualization, L.K., T.A. and D.O.; methodology, L.K., C.S., C.B. and T.A.; software, L.K.; validation, L.K., T.A. and D.O.; formal analysis, L.K. and T.A.; investigation, T.A., D.O. and L.K.; resources, L.K., C.S., C.B., J.R.; data curation, L.K., C.B., C.S., J.R.; writing—original draft preparation, T.A. and L.K.; writing—review and editing, C.S., C.B., L.K., V.F.K., J.R., D.O. and T.A.; visualization, L.K. and T.A.; supervision, C.B., C.S., L.K.; project administration, C.B., C.S. and L.K.; All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Smallridge, R.C.; Ain, K.B.; Asa, S.L.; Bible, K.C.; Brierley, J.D.; Burman, K.D.; Kebebew, E.; Lee, N.Y.; Nikiforov, Y.E.; Rosenthal, M.S.; et al. American Thyroid Association Guidelines for management of patients with anaplastic thyroid cancer. *Thyroid* **2012**, *22*, 1104–1139. [CrossRef] [PubMed]
2. Salehian, B.; Liem, S.Y.; Mojazi Amiri, H.; Maghami, E. Clinical trials in management of anaplastic thyroid carcinoma; Progressions and set backs: A systematic review. *Int. J. Endocrinol. Metab.* **2019**, *17*. [CrossRef] [PubMed]
3. Haymart, M.R.; Banerjee, M.; Yin, H.; Worden, F.; Griggs, J.J. Marginal treatment benefit in anaplastic thyroid cancer. *Cancer* **2013**, *119*, 3133–3139. [CrossRef] [PubMed]
4. Sugitani, I.; Onoda, N.; Ito, K.; Suzuki, S. Management of anaplastic thyroid carcinoma: The fruits from the ATC Research Consortium of Japan. *J. Nippon Med. Sch.* **2018**, *85*, 18–27. [CrossRef]
5. Pezzi, T.A.; Mohamed, A.S.R.; Sheu, T.; Blanchard, P.; Sandulache, V.C.; Lai, S.Y.; Cabanillas, M.E.; Williams, M.D.; Pezzi, C.M.; Lu, C.; et al. Radiation therapy dose is associated with improved survival for unresected anaplastic thyroid carcinoma: Outcomes from the National Cancer Data Base. *Cancer* **2017**, *123*, 1653–1661. [CrossRef]
6. Liu, T.-R.; Xiao, Z.-W.; Xu, H.-N.; Long, Z.; Wei, F.-Q.; Zhuang, S.-M.; Sun, X.-M.; Xie, L.-E.; Mu, J.-S.; Yang, A.-K.; et al. Treatment and prognosis of anaplastic thyroid carcinoma: A clinical study of 50 cases. *PLoS ONE* **2016**, *11*, e164840. [CrossRef]
7. Keutgen, X.M.; Sadowski, S.M.; Kebebew, E. Management of anaplastic thyroid cancer. *Gland Surg.* **2015**, *4*, 44–51. [CrossRef]
8. Simões-Pereira, J.; Capitão, R.; Limbert, E.; Leite, V. Anaplastic thyroid cancer: Clinical picture of the last two decades at a single oncology referral centre and novel therapeutic options. *Cancers* **2019**, *11*, 1188. [CrossRef]

9. Rades, D.; Janssen, S.; Käsmann, L.; Bolm, L.; Schild, S.E. Outcomes after irradiation of epidural spinal cord compression due to metastatic thyroid cancer. *Anticancer Res.* **2016**, *36*, 2035–2039. [PubMed]
10. Onoda, N.; Sugitani, I.; Ito, K.; Suzuki, A.; Higashiyama, T.; Fukumori, T.; Suganuma, N.; Masudo, K.; Nakayama, H.; Uno, A.; et al. Evaluation of the 8th edition TNM classification for anaplastic thyroid carcinoma. *Cancers* **2020**, *12*, 552. [CrossRef]
11. Filetti, S.; Durante, C.; Hartl, D.; Leboulleux, S.; Locati, L.D.; Newbold, K.; Papotti, M.G.; Berruti, A. Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. *Ann. Oncol.* **2019**, *30*, 1856–1883. [CrossRef] [PubMed]
12. Sun, C.; Li, Q.; Hu, Z.; He, J.; Li, C.; Li, G.; Tao, X.; Yang, A. Treatment and prognosis of anaplastic thyroid carcinoma: Experience from a single institution in China. *PLoS ONE* **2013**, *8*, e80011. [CrossRef] [PubMed]
13. Lee, J.-H.; Ahn, H.K.; Seok, J.Y.; Lee, K.-C.; Chun, Y.S.; Chung, Y.S.; Lee, Y.D. Optimal combination of treatment modality to increase survival in patients with anaplastic thyroid carcinoma. *Medicine* **2018**, *97*. [CrossRef] [PubMed]
14. Rao, S.N.; Zafereo, M.; Dadu, R.; Busaidy, N.L.; Hess, K.; Cote, G.J.; Williams, M.D.; William, W.N.; Sandulache, V.; Gross, N.; et al. Patterns of treatment failure in anaplastic thyroid carcinoma. *Thyroid* **2017**, *27*, 672–681. [CrossRef]
15. Corrigan, K.L.; Williamson, H.; Elliott Range, D.; Niedzwiecki, D.; Brizel, D.M.; Mowery, Y.M. Treatment outcomes in anaplastic thyroid cancer. *J. Thyroid Res.* **2019**, *2019*. [CrossRef]
16. Wendler, J.; Kroiss, M.; Gast, K.; Kreissl, M.C.; Allelein, S.; Lichtenauer, U.; Blaser, R.; Spitzweg, C.; Fassnacht, M.; Schott, M.; et al. Clinical presentation, treatment and outcome of anaplastic thyroid carcinoma: Results of a multicenter study in Germany. *Eur. J. Endocrinol.* **2016**, *175*, 521–529. [CrossRef]
17. Zivaljevic, V.; Tausanovic, K.; Paunovic, I.; Diklic, A.; Kalezic, N.; Zoric, G.; Sabljak, V.; Vekic, B.; Zivic, R.; Marinkovic, J.; et al. Age as a prognostic factor in anaplastic thyroid cancer. *Int. J. Endocrinol.* **2014**, *2014*, 1–5. [CrossRef]
18. Kebebew, E.; Greenspan, F.S.; Clark, O.H.; Woeber, K.A.; McMillan, A. Anaplastic thyroid carcinoma. *Cancer* **2005**, *103*, 1330–1335. [CrossRef]
19. Scharf, A.-C.; Gronewold, J.; Dahlmann, C.; Schlitzer, J.; Kribben, A.; Gerken, G.; Frohnhofen, H.; Dodel, R.; Hermann, D.M. Clinical and functional patient characteristics predict medical needs in older patients at risk of functional decline. *BMC Geriatr.* **2020**, *20*, 1–11. [CrossRef]
20. Kaesmann, L.; Janssen, S.; Rades, D. Karnofsky performance score, radiation dose and nodal status predict survival of elderly patients irradiated for limited-disease small-cell lung cancer. *Anticancer Res.* **2016**, *36*, 4177–4180. [PubMed]
21. Oliinyk, D.; Augustin, T.; Koehler, V.F.; Rauch, J.; Belka, C.; Spitzweg, C.; Käsmann, L. Hypofractionated radiotherapy for anaplastic thyroid cancer: Systematic review and pooled analysis. *Cancers* **2020**, *12*, 2506. [CrossRef] [PubMed]
22. Fan, D.; Ma, J.; Bell, A.C.; Groen, A.H.; Olsen, K.S.; Lok, B.H.; Leeman, J.E.; Anderson, E.; Riaz, N.; McBride, S. Outcomes of multimodal therapy in a large series of patients with anaplastic thyroid cancer. *Cancer* **2019**, *126*, 444–452. [CrossRef] [PubMed]
23. Sugitani, I.; Kasai, N.; Fujimoto, Y.; Yanagisawa, A. Prognostic factors and therapeutic strategy for anaplastic carcinoma of the thyroid. *World J. Surg.* **2001**, *25*, 617–622. [CrossRef] [PubMed]
24. Pierie, J.-P.E.N.; Muzikansky, A.; Gaz, R.D.; Faquin, W.C.; Ott, M.J. The effect of surgery and radiotherapy on outcome of anaplastic thyroid carcinoma. *Ann. Surg. Oncol.* **2002**, *9*, 57–64. [CrossRef]
25. Kihara, M.; Miyauchi, A.; Yamauchi, A.; Yokomise, H. Prognostic Factors of Anaplastic Thyroid Carcinoma. *Surg. Today* **2004**, *34*, 394–398. [CrossRef]
26. Brignardello, E.; Gallo, M.; Baldi, I.; Palestini, N.; Piovesan, A.; Grossi, E.; Ciccone, G.; Boccuzzi, G. Anaplastic thyroid carcinoma: Clinical outcome of 30 consecutive patients referred to a single institution in the past 5 years. *Eur. J. Endocrinol.* **2007**, *156*, 425–430. [CrossRef]
27. Kim, T.Y.; Kim, K.W.; Jung, T.S.; Kim, J.M.; Kim, S.W.; Chung, K.; Kim, E.Y.; Gong, G.; Oh, Y.L.; Cho, S.Y. Prognostic factors for Korean patients with anaplastic thyroid carcinoma. *Head Neck* **2007**, *29*, 765–772. [CrossRef]
28. Chen, J.; Tward, J.D.; Shrieve, D.C.; Hitchcock, Y.J. Surgery and radiotherapy improves survival in patients with anaplastic thyroid carcinoma: Analysis of the surveillance, epidemiology, and end results 1983–2002. *Am. J. Clin. Oncol.* **2008**, *31*, 460–464. [CrossRef]

29. Yau, T.; Lo, C.Y.; Epstein, R.J.; Lam, A.K.Y.; Wan, K.Y.; Lang, B.H. Treatment outcomes in anaplastic thyroid carcinoma: Survival improvement in young patients with localized disease treated by combination of surgery and radiotherapy. *Ann. Surg. Oncol.* **2008**, *15*, 2500. [CrossRef]
30. Bhatia, A.; Rao, A.; Ang, K.-K.; Garden, A.S.; Morrison, W.H.; Rosenthal, D.I.; Evans, D.B.; Clayman, G.; Sherman, S.I.; Schwartz, D.L. Anaplastic thyroid cancer: Clinical outcomes with conformal radiotherapy. *Head Neck* **2010**, *32*, 829–836. [CrossRef]
31. Roche, B.; Larroumets, G.; Dejax, C.; Kwiatkowsi, F.; Desbiez, F.; Thieblot, P.; Tauveron, I. Epidemiology, clinical presentation, treatment and prognosis of a regional series of 26 anaplastic thyroid carcinomas (ATC). Comparison with the literature. *Ann. Endocrinol.* **2010**, *71*, 38–45. [CrossRef] [PubMed]
32. Akaishi, J.; Sugino, K.; Kitagawa, W.; Nagahama, M.; Kameyama, K.; Shimizu, K.; Ito, K.; Ito, K. Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma. *Thyroid Off. J. Am. Thyroid Assoc.* **2011**, *21*, 1183–1189. [CrossRef] [PubMed]
33. Derbel, O.; Limem, S.; Ségura-Ferlay, C.; Lifante, J.-C.; Carrie, C.; Peix, J.-L.; Borson-Chazot, F.; Bournaud, C.; Droz, J.-P.; de la Fouchardière, C. Results of combined treatment of anaplastic thyroid carcinoma (ATC). *BMC Cancer* **2011**, *11*, 469. [CrossRef] [PubMed]
34. Sherman, E.J.; Lim, S.H.; Ho, A.L.; Ghossein, R.A.; Fury, M.G.; Shaha, A.R.; Rivera, M.; Lin, O.; Wolden, S.; Lee, N.Y.; et al. Concurrent doxorubicin and radiotherapy for anaplastic thyroid cancer: A critical re-evaluation including uniform pathologic review. *Radiother. Oncol.* **2011**, *101*, 425–430. [CrossRef] [PubMed]
35. Tashima, L.; Mitzner, R.; Durvesh, S.; Goldenberg, D. Dyspnea as a prognostic factor in anaplastic thyroid carcinoma. *Eur. Arch. Otorhinolaryngol.* **2012**, *269*, 1251–1255. [CrossRef] [PubMed]
36. Sugitani, I.; Miyauchi, A.; Sugino, K.; Okamoto, T.; Yoshida, A.; Suzuki, S. Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC research consortium of Japan cohort study of 677 patients. *World J. Surg.* **2012**, *36*, 1247–1254. [CrossRef]
37. Dumke, A.-K.; Pelz, T.; Vordermark, D. Long-term results of radiotherapy in anaplastic thyroid cancer. *Radiat. Oncol. Lond. Engl.* **2014**, *9*, 90. [CrossRef]
38. Mohebati, A.; DiLorenzo, M.; Palmer, F.; Patel, S.G.; Pfister, D.; Lee, N.; Tuttle, R.M.; Shaha, A.R.; Shah, J.P.; Ganly, I. Anaplastic Thyroid Carcinoma: A 25-year Single-Institution Experience. *Ann. Surg. Oncol.* **2014**, *21*, 1665–1670. [CrossRef]
39. Polistena, A.; Monacelli, M.; Lucchini, R.; Triola, R.; Conti, C.; Avenia, S.; Rondelli, F.; Bugiantella, W.; Barillaro, I.; Sanguinetti, A.; et al. The role of surgery in the treatment of thyroid anaplastic carcinoma in the elderly. *Int. J. Surg.* **2014**, *12*, S170–S176. [CrossRef]
40. Lo, T.E.; Jimeno, C.A.; Paz-Pacheco, E. Anaplastic thyroid cancer: Experience of the Philippine general hospital. *Endocrinol. Metab.* **2015**, *30*, 195–200. [CrossRef]
41. Paunovic, I.; Sipetic, S.; Zoric, G.; Diklic, A.; Savic, D.; Marinkovic, J.; Zivaljevic, V. Survival and prognostic factors of anaplastic thyroid carcinoma. *Acta Chir. Belg.* **2015**, *115*, 62–67. [CrossRef] [PubMed]
42. Baek, S.-K.; Lee, M.-C.; Hah, J.H.; Ahn, S.-H.; Son, Y.-I.; Rho, Y.-S.; Chung, P.-S.; Lee, Y.-S.; Koo, B.S.; Jung, K.-Y.; et al. Role of surgery in the management of anaplastic thyroid carcinoma: Korean nationwide multicenter study of 329 patients with anaplastic thyroid carcinoma, 2000 to 2012. *Head Neck* **2017**, *39*, 133–139. [CrossRef] [PubMed]
43. Glaser, S.M.; Mandish, S.F.; Gill, B.S.; Balasubramani, G.K.; Clump, D.A.; Beriwal, S. Anaplastic thyroid cancer: Prognostic factors, patterns of care, and overall survival. *Head Neck* **2016**, *38*, E2083–E2090. [CrossRef] [PubMed]
44. Käsmann, L.; Bolm, L.; Janssen, S.; Rades, D. Prognostic factors for survival in patients treated with multimodal therapy for anaplastic thyroid cancer. *Anticancer Res.* **2016**, *36*, 4697–4700. [CrossRef]
45. Lennon, P.; Deady, S.; Healy, M.L.; Toner, M.; Kinsella, J.; Timon, C.I.; O'Neill, J.P. Anaplastic thyroid carcinoma: Failure of conventional therapy but hope of targeted therapy. *Head Neck* **2016**, *38*, E1122–E1129. [CrossRef]
46. Hvilsom, G.B.; Londero, S.C.; Hahn, C.H.; Schytte, S.; Pedersen, H.B.; Christiansen, P.; Kiss, K.; Larsen, S.R.; Jespersen, M.L.; Lelkaitis, G.; et al. Anaplastic thyroid carcinoma in Denmark 1996–2012: A national prospective study of 219 patients. *Cancer Epidemiol.* **2018**, *53*, 65–71. [CrossRef]

47. Jacobsen, A.-B.; Grøholt, K.K.; Lorntzsen, B.; Osnes, T.A.; Falk, R.S.; Sigstad, E. Anaplastic thyroid cancer and hyperfractionated accelerated radiotherapy (HART) with and without surgery. *Eur. Arch. Otorhinolaryngol.* **2017**, *274*, 4203–4209. [CrossRef]
48. Park, J.W.; Choi, S.H.; Yoon, H.I.; Lee, J.; Kim, T.H.; Kim, J.W.; Lee, I.J. Treatment outcomes of radiotherapy for anaplastic thyroid cancer. *Radiat. Oncol. J.* **2018**, *36*, 103–113. [CrossRef]
49. Takahashi, N.; Matsushita, H.; Umezawa, R.; Yamamoto, T.; Ishikawa, Y.; Katagiri, Y.; Tasaka, S.; Takeda, K.; Fukui, K.; Kadoya, N.; et al. Hypofractionated radiotherapy for anaplastic thyroid carcinoma: 15 years of experience in a single institution. *Eur. Thyroid J.* **2019**, *8*, 24–30. [CrossRef]
50. Huang, N.; Shi, X.; Lei, B.; Wei, W.; Lu, Z.; Yu, P.; Wang, Y.; Ji, Q.; Wang, Y. An update of the appropriate treatment strategies in anaplastic thyroid cancer: A population-based study of 735 patients. *Int. J. Endocrinol.* **2019**, *2019*, 1–7. [CrossRef]
51. Li, M.; Gu, S.; Mao, R.; Ning, Y.; Trivedi, N.; Siddiqui, A.; Li, P.; Huo, L. County median family income is an independent prognostic factor for stage IV anaplastic thyroid cancer. *Anticancer Res.* **2019**, *39*, 949–956. [CrossRef] [PubMed]
52. de Ridder, M.; van Dijkum, E.N.; Engelsman, A.; Kapiteijn, E.; Klümpen, H.-J.; Rasch, C.R.N. Anaplastic thyroid carcinoma: A nationwide cohort study on incidence, treatment and survival in the Netherlands over 3 decades. *Eur. J. Endocrinol.* **2020**, *183*, 203–209. [CrossRef] [PubMed]
53. Gui, W.; Zhu, W.; Lu, W.; Shang, C.; Zheng, F.; Lin, X.; Li, H. Development and validation of a prognostic nomogram to predict overall survival and cancer-specific survival for patients with anaplastic thyroid carcinoma. *PeerJ* **2020**, *8*, e9173. [CrossRef]
54. Lin, B.; Ma, H.; Ma, M.; Zhang, Z.; Sun, Z.; Hsieh, I.; Okenwa, O.; Guan, H.; Li, J.; Lv, W. The incidence and survival analysis for anaplastic thyroid cancer: A SEER database analysis. *Am. J. Transl. Res.* **2019**, *11*, 5888–5896. [PubMed]
55. Saeed, N.A.; Kelly, J.R.; Deshpande, H.A.; Bhatia, A.K.; Burtness, B.A.; Judson, B.L.; Mehra, S.; Edwards, H.A.; Yarbrough, W.G.; Peter, P.R.; et al. Adjuvant external beam radiotherapy for surgically resected, nonmetastatic anaplastic thyroid cancer. *Head Neck* **2020**, *42*, 1031–1044. [CrossRef] [PubMed]
56. Wächter, S.; Wunderlich, A.; Roth, S.; Mintziras, I.; Maurer, E.; Hoffmann, S.; Verburg, F.A.; Fellinger, S.A.; Holzer, K.; Bartsch, D.K.; et al. Individualised multimodal treatment strategies for anaplastic and poorly differentiated thyroid cancer. *J. Clin. Med.* **2018**, *7*, 115. [CrossRef]
57. Lim, S.M.; Shin, S.-J.; Chung, W.Y.; Park, C.S.; Nam, K.-H.; Kang, S.-W.; Keum, K.C.; Kim, J.H.; Cho, J.Y.; Hong, Y.K.; et al. Treatment outcome of patients with anaplastic thyroid cancer: A single center experience. *Yonsei Med. J.* **2012**, *53*, 352–357. [CrossRef]
58. Stavas, M.J.; Shinohara, E.T.; Attia, A.; Ning, M.S.; Friedman, J.M.; Cmelak, A.J. short course high dose radiotherapy in the treatment of anaplastic thyroid carcinoma. *J. Thyroid Res.* **2014**, *2014*. [CrossRef]
59. Busnardo, B.; Daniele, O.; Pelizzo, M.R.; Mazzarotto, R.; Nacamulli, D.; DeVido, D.; Mian, C.; Girelli, M.E. A multimodality therapeutic approach in anaplastic thyroid carcinoma: Study on 39 patients. *J. Endocrinol. Investig.* **2000**, *23*, 755–761. [CrossRef]
60. So, K.; Smith, R.E.; Davis, S.R. Radiotherapy in anaplastic thyroid carcinoma: An Australian experience. *J. Med. Imaging Radiat. Oncol.* **2017**, *61*, 279–287. [CrossRef]
61. Aslan, Z.A.T.; Granados-García, M.; Luna-Ortiz, K.; Guerrero-Huerta, F.J.; Gómez-Pedraza, A.; Ñamendys-Silva, S.A.; Meneses-García, A.; Ordoñez-Mosquera, J.M. Anaplastic thyroid cancer: Multimodal treatment results. *Ecancermedicalscience* **2014**, *8*. [CrossRef]
62. Crevoisier, R.D.; Baudin, E.; Bachelot, A.; Leboulleux, S.; Travagli, J.-P.; Caillou, B.; Schlumberger, M. Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy. *Int. J. Radiat. Oncol. Biol. Phys.* **2004**, *60*, 1137–1143. [CrossRef] [PubMed]
63. Rades, D.; Manig, L.; Janssen, S.; Schild, S.E. Factors impacting the overall survival of patients irradiated for invasive carcinoma of the urinary bladder. *In Vivo* **2017**, *31*, 741–744. [CrossRef] [PubMed]
64. Rades, D.; Bolm, L.; Kaesmann, L.; Bartscht, T. Karnofsky performance score is predictive of survival after palliative irradiation of metastatic bile duct cancer. *Anticancer Res.* **2017**, *37*, 949–951. [CrossRef]
65. Edwards, B.J.; Zhang, X.; Sun, M.; Song, J.; Khalil, P.; Karuturi, M.S.; Pang, L.; Geng, Y.; Dinney, C.P.; Valero, V. Overall survival in older patients with cancer. *BMJ Support. Palliat. Care* **2020**, *10*, 25–35. [CrossRef]

66. Brignardello, E.; Palestini, N.; Felicetti, F.; Castiglione, A.; Piovesan, A.; Gallo, M.; Freddi, M.; Ricardi, U.; Gasparri, G.; Ciccone, G.; et al. Early surgery and survival of patients with anaplastic thyroid carcinoma: Analysis of a case series referred to a single institution between 1999 and 2012. *Thyroid* **2014**, *24*, 1600–1606. [CrossRef]
67. He, X.; Li, D.; Hu, C.; Wang, Z.; Ying, H.; Wu, Y. Outcome after intensity modulated radiotherapy for anaplastic thyroid carcinoma. *BMC Cancer* **2014**, *14*, 235. [CrossRef]
68. Tiedje, V.; Stuschke, M.; Weber, F.; Dralle, H.; Moss, L.; Führer, D. Anaplastic thyroid carcinoma: Review of treatment protocols. *Endocr. Relat. Cancer* **2018**, *25*, R153–R161. [CrossRef]
69. Haddad, R.I.; Kandeel, F.; Scheri, R.P. NCCN Guidelines Index Table of Contents Discussion. 2019, p. 137. Available online: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf (accessed on 28 March 2020).

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).

7. Paper III

in vivo *35*: 461-465 (2021)
doi:10.21873/invivo.12279

Radiation to the Primary Tumor in Metastatic Anaplastic Thyroid Cancer

TERESA AUGUSTIN[1], DMYTRO OLIINYK[1], JOSEFINE RAUCH[1], VIKTORIA FLORENTINE KOEHLER[2], CHRISTINE SPITZWEG[2,3], CLAUS BELKA[1,3] and LUKAS KÄSMANN[1,3]

[1]*Department of Radiation Oncology, University Hospital, LMU Munich, Munich, Germany;*
[2]*Department of Internal Medicine IV, University Hospital, LMU Munich, Munich, Germany;*
[3]*German Cancer Consortium (DKTK), Partner Site Munich, Munich, Germany*

Abstract. *Background/Aim: Metastatic anaplastic thyroid cancer is associated with a dismal prognosis. We evaluated outcome and prognostic factors in patients receiving radiation to the primary tumor in metastatic anaplastic thyroid cancer (ATC). Patients and Methods: All consecutive patients with metastatic ATC (n=20) undergoing irradiation between 2009 and 2019 for anaplastic thyroid cancer were investigated. Results: Median survival time and median progression-free survival were 2 (range=1-22) and 2 (1-20) months. In univariate analyses, surgery, concurrent or sequential chemotherapy and higher radiation dose escalation (>39 Gy) were correlated with longer overall survival (p=0.005, p=0.018 and p=0.038), respectively. Karnofsky performance status >70% showed a trend of longer survival time (p=0.062). Limited metastatic disease, surgery and concurrent/sequential chemotherapy are correlated with longer progression-free survival times (p=0.043, p=0.024 and p=0.039), respectively. Conclusion: Radiation to the primary tumor in metastatic anaplastic thyroid cancer is safe and offers durable local control. Treatment intensification including concurrent or sequential chemotherapy and radiation dose escalation were associated with longer survival rates and should be considered in selected patients with metastatic disease.*

Anaplastic thyroid cancer (ATC) is an orphan disease with a dismal prognosis (1-6). Median survival times range between 3 and 16 months depending on Union for International Cancer Control tumor–node–metastasis (UICC TNM) stage (7-9). National and international guidelines recommend that ATC patients with stage IVA/B should be considered for radical surgery if negative pathological margins (R0/R1) can be achieved and should be avoided if there is a high chance of gross residual disease (R2) (2-5).

However, the majority of ATC patients are considered to be inoperable due to locally advanced disease and comorbidities. So far, no standard treatment regimen has been successfully established in stage IVC (4, 5).

Local radiotherapy (RT) should always be considered as part of the initial multimodal therapy approach to improve overall survival (OS) (6, 9-11) and provide local and symptom control in order to maintain quality of life. However, it is a matter of debate if local RT is still recommended in metastatic disease where aggressive systemic therapy has to be weighed against benefits from local control and limited systemic approaches.

The aim of the present study was to evaluate outcome and prognostic factors in patients receiving radiation to primary tumor of metastatic anaplastic thyroid cancer.

Patients and Methods

Study population. The medical charts of 20 consecutive patients with metastatic anaplastic thyroid cancer treated with irradiation to primary tumor between 2009 and 2019 were reviewed. Patient and treatment characteristics are summarized in Table I. The Institutional Research Ethical Review Board approved the study (approval number: 19-885).

Diagnostics and treatment. ATC was histologically confirmed in all patients and diagnosed as stage IVC according to the revised 8th edition of the UICC TNM classification (7). A lobectomy was performed in two (10%) patients and three (15%) patients had received a total thyroidectomy. Chemotherapy was administered in 9 (45%) patients, of which 5 (25%) patients received concurrent chemotherapy with carboplatin AUC 2 with Paclitaxel 50 mg/m^2 weekly, which has been the standard at our Institution in the recent years, and 3 patients (15%) received concurrent chemotherapy with

This article is freely accessible online.

Correspondence to: Lukas Käsmann, Department of Radiotherapy and Radiation Oncology, Ludwig-Maximilians-Universität, Marchioninistraße 15, 81377 München, Germany. Tel: +49 89440073770, Fax: +49 89440076770, e-mail: lukas.kaesmann@med.uni-muenchen.de

Key Words: ATC, anaplastic thyroid cancer, metastatic, irradiation, survival.

in vivo *35*: 461-465 (2021)

doxorubicin (10 or 20 mg/m2) weekly. Sequential chemotherapy (doxorubicin/cisplatin) was administered in one (5%) patient before radiation. Three-dimensional conformal radiotherapy (3D-CRT) technique was administered in 13 (65%) patients and 7 (35%) patients received intensity modulated radiation therapy (IMRT). The median radiation dose in equivalent dose in 2 Gy fractions (EQD2) was 42 (range=5-70) Gy. Seven potential patient- and treatment-related features, namely age, gender, Karnofsky performance status (KPS), number of involved metastatic sites, surgery, concurrent and sequential chemotherapy and radiation dose escalation were analysed for their impact on OS and progression-free survival (PFS). Treatment-related side-effects were evaluated using Common Terminology Criteria for Adverse events (CTCAE) version 4.

Statistical analysis. Statistical analyses were performed using SPSS statistics 25 (IBM, New York City, NY, SA). The log-rank test was used to compare subgroups. All significant variables in univariate analysis were included in a multivariate analysis (Cox regression). OS was defined as the time between diagnosis and death. PFS was defined as the time between diagnosis and the development of local relapse, distant metastases or death from all causes.

For all statistical analyses, a p-value <0.05 was considered statistically significant.

Results

Median survival time was 2 (range=1-22) months. Survival at 1, 3 and 12 months of the entire cohort was 65, 30 and 5%, respectively. No local progression was observed in the first 12 months after radiotherapy. Progression-free survival was 2 (range=1-20) months. In univariate analyses, surgery (p=0.005), sequential or concurrent chemotherapy (p=0.018) and radiation dose escalation (>39 Gy, p=0.038) resulted in improved OS (Table II), respectively. Karnofsky performance status >70% showed a trend for longer survival time (p=0.062). On multivariate analysis, no factor achieved significance for OS. Limited metastatic sites (1 *vs*. 2-4 sites, p=0.043), surgery (p=0.024) and chemotherapy (p=0.039) are associated with improved PFS (Table III). On multivariate analysis for PFS no factor achieved significance.

Acute toxicity (grade 3) of dysphagia, dyspnea, dermatitis, mucositis and dysphonia were found in 20%, 30%, 5%, 5% and 10% of patients, respectively. CTCAE grade 4/5 was not observed.

Discussion

The treatment of patients with metastatic ATC should be planned in a multidisciplinary expert team also considering prognostic factors, which allow estimating the patient's prognosis (1, 10, 12). Systemic treatment remains the main treatment of metastatic ATC, but usually results in low response rates and significant toxicities. Treatment with paclitaxel or doxorubicin or combined treatment approaches (*e.g.* carboplatin/paclitaxel, docetaxel/doxorubicin) are recommended (5).

Table I. *Patient- and treatment-related characteristics*.

	N	%
Age, years		
<73	10	50
≥73	10	50
Gender		
Female	11	55
Male	9	45
Karnofsky performance status, %		
≤70	14	70
>70	6	30
T stage		
3	1	5
4	19	95
N category		
0	5	25
1	15	75
Number of metastatic sites		
1	11	55
2-4	9	45
Metastatic sites		
Pulmonary	19	95
Distant lymph node	8	40
Bone	3	15
Brain	1	5
Liver	1	5
Surgery		
No	15	75
Yes	5	25
Chemotherapy		
No	11	55
Yes	9	45
Radiation dose, Gy		
≤39	8	40
>39	12	60

T: Tumor, N: nodal, Gy: Gray.

Tumor-related complications such as airway or esophageal obstruction, hemorrhage and vocal cord paralysis can be lethal and should be taken into account for shared-decision making (2-5). Therefore, prognostic factors that indicate the effect of radiotherapy on local control and survival are important to identify high-risk patients who do not achieve a satisfying outcome and may benefit from treatment intensification such as radiation dose escalation or concurrent chemotherapy.

Several studies investigated potential prognostic factors in ATC such as age, presence of acute symptoms, leukocytosis, large local tumors, resection status and distant metastasis (1, 13, 14). Data about prognostic factors in stage IVC are still limited (8, 13, 15).

The present study aimed to evaluate outcome and prognostic factors in patients with metastatic anaplastic thyroid cancer that received radiation to the primary tumor. As a result, cervical irradiation appears to be effective and offers durable local

Table II. *Uni- and multivariate analyses of overall survival*.

	At 1 month,%	At 3 months, %	At 12 months, %	*p*-Value (univariate analyses)	*p*-Value (multivariate analyses)
Age, years					
<73	60	30	10		
≥73	70	30	0	0.47	
Gender					
Female	64	27	9		
Male	67	33	0	0.802	
Karnofsky performance status, %					
≤70	57	21	0		
>70	83	50	17	0.062	
Metastatic sites					
1	73	36	9		
2-4	56	22	0	0.322	
Surgery					
No	53	13	0		
Yes	100	80	20	0.005	0.051
Chemotherapy					
No	44	11	0		
Yes	82	46	9	0.018	0.988
Radiation dose, Gy					
≤39	38	13	0		
>39	83	42	8	0.038	0.415

Gy: Gray.

Table III. *Uni- and multivariate analyses of progression-free survival*.

	At 1 Month, %	At 3 months, %	At 12 months, %	*p*-Value (univariate analyses)	*p*-Value (multivariate analyses)
Age, years					
<73	50	20	10	0.926	
≥73	70	30	0		
Gender					
Female	64	18	9		
Male	56	22	0	0.896	
Karnofsky performance status, %					
≤70	50	14	0		
>70	83	33	17	0.192	
N stage					
0	60	40	20		
1	60	13	0	0.263	
Metastatic sites					
1	64	36	9		
2-4	56	0	0	0.043	0.336
Surgery					
No	47	7	0		
Yes	100	60	20	0.024	0.23
Chemotherapy					
No	44	0	0		
Yes	73	36	9	0.039	0.598
Radiation dose, Gy					
≤39	38	0	0		
>39	75	33	8	0.075	

Gy: Gray.

control of the disease. In our analysis surgery, chemotherapy (carboplatin/paclitaxel or doxorubicin) and radiation dose escalation (>39 Gy) were correlated with longer OS. This is consistent with the findings by Wendler *et al*. who reported a significant association of multimodal treatment approaches with a survival benefit in ATC stage IVC patients (1) as well as the study of Sugitani *et al*. with 223 ATC patients in stage IVC which found that radical surgery (p=0.0002), dose escalated radiotherapy (≥40 Gy) (p<0.0001) and chemotherapy (p<0.0001) were correlated with longer survival rates (13).

A National Cancer Data Base (NCDB) study of 606 patients with ATC stage IVC found a dose-survival correlation in patients receiving 60 to 75 Gy compared to 45 to 59.9 Gy (15). These data go along with the findings of our present study.

Despite local and symptom control, pattern of failure in ATC tends to be metastatic progression, which is consistent with our study (16). We found that a limited number of metastatic sites ('oligometastatic disease') appears to be a prognostic factor for PFS (see Table III) and that these patients may benefit from more aggressive treatment approaches which offer reliable local control and longer OS.

Treatment-related side-effects were manageable according to our study. However, treatment intensification should be discussed in multidisciplinary teams including surgeons, radiation oncologists, endocrinologists, medical oncologists, and palliative care teams.

Due to a substantial increase of druggable tumor-specific molecular aberrations in the past decade, molecular profiling has become an integral part of diagnosis and therapy in oncology, gaining more and more importance in the treatment of ATC. The most frequently investigated single agents or agents in combined treatment approaches are multikinase inhibitors (*e.g*. lenvatinib, sorafenib), PI3K/mTOR inhibitors (*e.g*. everolismus), vascular-targeting agents (*e.g*. fosbretabulin), BRAF-inhibitors (*e.g*. dabrafenib) and checkpoint inhibitors (*e.g*. pembrolizumab, spartalizumab) (17-23).

The combination of BRAF-inhibitor dabrafenib and MEK-inhibitor trametinib achieved approval by the Food and Drug Administration (FDA) in 2018 based on the promising results of a phase II study comprising BRAFV600E-mutated ATC (21). The overall response rate in the ATC-subgroup was 61%, of which 57% experienced a partial and 4% a complete response. In addition, several checkpoint inhibitors such as pembrolizumab, spartalizumab and durvalumab alone or in combination with conventional treatment regimens (RT, ChT) have been investigated (22-24).

Recently, the combination of lenvatinib with pembrolizumab has achieved excellent results in metastatic ATC (25). However, larger trials investigating this combined treatment approach are ongoing and highly anticipated (26).

Several limitations must be considered in interpreting the results of our study such as the retrospective design and, therefore, a risk of including hidden selection biases. In addition, the patient cohort is relatively small with a long recruitment period. However, ATC is an orphan disease and stage IVC is associated with a dismal prognosis. We found that local irradiation offers durable local control in metastatic ATC patients and identified several prognostic factors in this setting. As a result, we are convinced that our study may help physicians to tailor personalized treatment approaches.

In summary, treatment-related side-effects appear to be manageable and therapy intensification including concurrent or sequential chemotherapy and radiation dose escalation were correlated with longer survival rates.

Conclusion

Radiation to the primary tumor in metastatic anaplastic thyroid cancer is safe and offers durable local control. Treatment intensification including concurrent or sequential chemotherapy and radiation dose escalation were correlated with longer survival rates and should be considered in selected patients with metastatic disease.

Conflicts of Interest

There are no conflicts of interest to declare regarding this study.

Authors' Contributions

Conception and Design: L.K., T.A., D.O.; Administrative support: C.B., C.S., L.K.; Provision of study materials or patients: L.K., C.S., C.B., J.R.; Collection and assembly of data: L.K., T.A., D.O.; Data analysis and interpretation: L.K., T.A., D.O.; Manuscript writing: All authors; Final approval of manuscript: All Authors.

References

1 Wendler J, Kroiss M, Gast K, Kreissl MC, Allelein S, Lichtenauer U, Blaser R, Spitzweg C, Fassnacht M and Schott M: Clinical presentation, treatment and outcome of anaplastic thyroid carcinoma: results of a multicenter study in Germany. Eur J Endocrinol *175(6)*: 521-529, 2016. PMID: 27926471. DOI: 10.1530/EJE-16-0574

2 Smallridge RC, Ain KB, Asa SL, Bible KC, Brierley JD, Burman KD, Kebebew E, Lee NY, Nikiforov YE and Rosenthal MS: American Thyroid Association guidelines for management of patients with anaplastic thyroid cancer. Thyroid *22(11)*: 1104-1139, 2012. PMID: 23130564. DOI: 10.1089/thy.2012.0302

3 Perros P, Boelaert K, Colley S, Evans C, Evans RM, Gerrard BA G, Gilbert J, Harrison B, Johnson SJ and Giles TE: Guidelines for the management of thyroid cancer. Clin Endocrinol (Oxf) *81(Suppl 1)*: 1-122, 2014. PMID: 24989897. DOI: 10.1111/cen.12515

4 Haddad R, Lydiatt W, Bischoff L, Busaidy N, Byrd D, Callender G, Dickson P, Duh Q, Ehya H and Haymart M: NCCN clinical practive guidelines in oncology (NCCN guidelines): thyroid carcinoma. Version 1, 2019. NCCN 2019. Available at: https://www.nccn.org/professionals/physician_gls/pdf/thyroid.pdf [Last accessed July 1, 2019]

5 Filetti S, Durante C, Hartl D, Leboulleux S, Locati L, Newbold K, Papotti M, Berruti A: Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol *30(12)*: 1856-1883, 2019. PMID: 31549998. DOI: 10.1093/annonc/mdz400
6 Oliinyk D, Augustin T, Koehler VF, Rauch J, Belka C, Spitzweg C and Käsmann L: Hypofractionated radiotherapy for anaplastic thyroid cancer: Systematic review and pooled analysis. Cancers *12(9)*: 2506, 2020. PMID: 32899355. DOI: 10.3390/cancers 12092506
7 Brierley JD, Gospodarowicz MK and Wittekind C: TNM classification of malignant tumours. Chichester, West Sussex, UK Hoboken, Wiley Blackwell/John Wiley & Sons, Inc, 2017.
8 Onoda N, Sugitani I, Ito K, Suzuki A, Higashiyama T, Fukumori T, Suganuma N, Masudo K, Nakayama H and Uno A: Evaluation of the 8th edition TNM classification for anaplastic thyroid carcinoma. Cancers *12(3)*: 552, 2020. PMID: 32120853. DOI: 10.3390/cancers12030552
9 Augustin T, Oliinyk D, Köhler VF, Rauch J, Belka C, Spitzweg C and Käsmann L: Clinical outcome and toxicity in the treatment of anaplastic thyroid cancer in elderly patients. J Clin Med *9(10)*: 3231, 2020. PMID: 33050286. DOI: 10.3390/jcm9103231
10 Käsmann L, Bolm L, Janssen S and Rades D: Prognostic factors for survival in patients treated with multimodal therapy for anaplastic thyroid cancer. Anticancer Res *36(9)*: 4697-4700, 2016. PMID: 27630315. DOI: 10.21873/anticancerres.11023
11 Fan D, Ma J, Bell AC, Groen AH, Olsen KS, Lok BH, Leeman JE, Anderson E, Riaz N and McBride S: Outcomes of multimodal therapy in a large series of patients with anaplastic thyroid cancer. Cancer *126(2)*: 444-452, 2020. PMID: 31593317. DOI: 10.1002/cncr.32548
12 Rades D, Janssen S, Käsmann L, Bolm L and Schild SE: Outcomes after irradiation of epidural spinal cord compression due to metastatic thyroid cancer. Anticancer Res *36(4)*: 2035-2039, 2016. PMID: 27069199.
13 Sugitani I, Miyauchi A, Sugino K, Okamoto T, Yoshida A and Suzuki S: Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC Research Consortium of Japan cohort study of 677 patients. World J Surg *36(6)*: 1247-1254, 2012. PMID: 22311136. DOI: 10.1007/s00268-012-1437-z
14 Käsmann L, Eze C and Manapov F: Stereotactic body radiation therapy (SBRT) combined with immune check-point inhibition (ICI) in advanced lung cancer: Which metastatic site should be irradiated to induce immunogenic cell death? Int J Radiat Oncol Biol Phys *108(1)*: 225-226, 2020. PMID: 32414625. DOI: 10.1016/j.ijrobp.2020.04.002
15 Pezzi TA, Mohamed AS, Sheu T, Blanchard P, Sandulache VC, Lai SY, Cabanillas ME, Williams MD, Pezzi CM and Lu C: Radiation therapy dose is associated with improved survival for unresected anaplastic thyroid carcinoma: outcomes from the National Cancer Data Base. Cancer *123(9)*: 1653-1661, 2017. PMID: 28026871. DOI: 10.1002/cncr.30493
16 Rao SN, Zafereo M, Dadu R, Busaidy NL, Hess K, Cote GJ, Williams MD, William WN, Sandulache V and Gross N: Patterns of treatment failure in anaplastic thyroid carcinoma. Thyroid *27(5)*: 672-681, 2017. PMID: 28068873. DOI: 10.1089/thy.2016.0395
17 Savvides P, Nagaiah G, Lavertu P, Fu P, Wright JJ, Chapman R, Wasman J, Dowlati A and Remick SC: Phase II trial of sorafenib in patients with advanced anaplastic carcinoma of the thyroid. Thyroid *23(5)*: 600-604, 2013. PMID: 23113752. DOI: 10.1089/thy.2012.0103
18 Tahara M, Kiyota N, Yamazaki T, Chayahara N, Nakano K, Inagaki L, Toda K, Enokida T, Minami H and Imamura Y: Lenvatinib for anaplastic thyroid cancer. Front Oncol *7*: 25, 2017. PMID: 28299283. DOI: 10.3389/fonc.2017.00025
19 Hanna GJ, Busaidy NL, Chau NG, Wirth LJ, Barletta JA, Calles A, Haddad RI, Kraft S, Cabanillas ME and Rabinowits G: Genomic correlates of response to everolimus in aggressive radioiodine-refractory thyroid cancer: a phase II study. Clin Cancer Res *24(7)*: 1546-1553, 2018. PMID: 29301825. DOI: 10.1158/1078-0432.CCR-17-2297
20 Mooney CJ, Nagaiah G, Fu P, Wasman JK, Cooney MM, Savvides PS, Bokar JA, Dowlati A, Wang D and Agarwala SS: A phase II trial of fosbretabulin in advanced anaplastic thyroid carcinoma and correlation of baseline serum-soluble intracellular adhesion molecule-1 with outcome. Thyroid *19(3)*: 233-240, 2019. PMID: 19265494. DOI: 10.1089/thy.2008.0321
21 Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JH, Soria JC, Wen PY, Zielinski C, Cabanillas ME and Urbanowitz G: Dabrafenib and trametinib treatment in patients with locally advanced or metastatic BRAF V600–mutant anaplastic thyroid cancer. J Clin Oncol *36(1)*: 7, 2018. PMID: 29072975. DOI: 10.1200/JCO.2017.73.6785
22 Chintakuntlawar AV, Yin J, Foote RL, Kasperbauer JL, Rivera M, Asmus E, Garces NI, Janus JR, Liu M and Ma DJ: A phase 2 study of pembrolizumab combined with chemoradiotherapy as initial treatment for anaplastic thyroid cancer. Thyroid *29(11)*: 1615-1622, 2019. PMID: 31595822. DOI: 10.1089/thy.2019.0086
23 Sherman EJ, Tsai CJ, Zhi WI, Fetten JV, Wu V, Ho AL, Riaz N, Pfister DG and Lee NY: Pilot study combining PD-L1 antibody durvalumab (D) with CTLA-4 antibody tremelimumab (T) and stereotactic body radiotherapy (SBRT) to treat metastatic anaplastic thyroid cancer (ATC). J Clin Oncol *37(Suppl 15)*: 6088, 2019. DOI: 10.1200/JCO.2019.37.15_suppl.6088
24 Capdevila J, Wirth LJ, Ernst T, Ponce Aix S, Lin C-C, Ramlau R, Butler MO, Delord J-P, Gelderblom H, Ascierto PA, Fasolo A, Führer D, Hütter-Krönke ML, Forde PM, Wrona A, Santoro A, Sadow PM, Szpakowski S, Wu H, Bostel G, Faris J, Cameron S, Varga A and Taylor M: PD-1 blockade in anaplastic thyroid carcinoma. J Clin Oncol *38(23)*: 2620-2627, 2020. PMID: 32364844. DOI: 10.1200/JCO.19.02727
25 Dierks C, Miething C, Thomusch O, von Bubnoff N and Duyster J: Lenvatinib and pembrolizumab as save and effective combination treatment in 8 patients with metastasized anaplastic (ATC) or poorly differentiated thyroid carcinoma (PDTC). Ann Oncol *29(Suppl 8)*: VIII646, 2018. DOI: 10.1093/annonc/mdy302.004
26 Dierks C, Seufert J, Ruf J, Duyster J, Thomusch O and Miething C and Zielke A: 1915P The lenvatinib/pembrolizumab combination induces long lasting and complete responses in patients with metastatic anaplastic or poorly differentiated thyroid carcinoma: Results from a retrospective study and first results from the prospective phase II ATLEP trial. Ann Oncol *31(4)*: S1085, 2020. DOI: 10.1016/j.annonc.2020.08.1403

Received November 16, 2020
Revised November 29, 2020
Accepted December 1, 2020

8. Paper IV

Journal of Cancer Research and Clinical Oncology (2023) 149:3527–3547
https://doi.org/10.1007/s00432-022-04223-7

RESEARCH

Role of surgery to the primary tumor in metastatic anaplastic thyroid carcinoma: pooled analysis and SEER-based study

Dmytro Oliinyk[1] · Teresa Augustin[1] · Josefine Rauch[1] · Viktoria Florentine Koehler[2] · Claus Belka[1,3] · Christine Spitzweg[2,3] · Lukas Käsmann[1,3]

Received: 11 June 2022 / Accepted: 18 July 2022 / Published online: 12 August 2022
© The Author(s) 2022, corrected publication 2022

Abstract

Purpose Anaplastic thyroid carcinoma (ATC) is an orphan disease with a fatal outcome. Surgery to the primary tumor in metastatic ATC is controversial. Determination of specific surgical techniques may help facilitate local control and, hence, beneficial overall and disease-specific survival.

Methods Using individualized patient data derived from our systematic review of literature and our single center study ($n=123$), conducting a Surveillance, Epidemiology, and End Results register (SEER)-based study ($n=617$) we evaluated surgery, its combination with systemic and local therapies in metastatic ATC.

Results Pooled cohort study showed surgery ($p<0.001$), RT ≥ 30 Gy ($p<0.001$), ChT ($p<0.001$) and multimodal treatment ($p=0.014$) to result in improved OS univariately. In the multivariate analysis, surgery (1.997 [1.162–3.433], $p=0.012$) and RT ≥ 30 Gy (1.877 [1.232–2.843], $p=0.012$) were independent predictors for OS. In SEER-based study of patients undergoing any tumor-directed treatment ($n=445$) total thyroidectomy ($p=0.031$), administration of ChT ($p=0.007$), RT ($p<0.001$), combination of surgery and RT ± ChT ($p<0.001$) and multimodal treatment ($p<0.001$) correlated with an improved DSS univariately. On the multivariate analysis, debulking surgery was an independent predictor for a worse outcome (HR 0.535, 95%CI 0.332–0.862, $p=0.010$), whereas RT administration correlated with a longer DSS (HR 2.316, 95%CI 1.362–3.939, $p=0.002$). Among operated patients from SEER register total thyroidectomy ($p=0.031$), ChT ($p=0.007$), RT ($p<0.001$), combination of surgery and RT ± ChT ($p<0.001$) and multimodal treatment ($p<0.001$) correlated with an improved DSS in the univariate analysis, whereas debulking surgery was inversely correlated with the DSS ($p<0.001$). On the multivariate analysis, debulking surgery was an independent predictor for a worse DSS (HR 0.535, 95%CI 0.332–0.862, $p=0.010$), whilst RT administration correlated with a longer DSS (HR 2.316, 95%CI 1.362–3.939, $p=0.002$).

Conclusions Surgery to the primary tumor with the aim of R0/R1 resection, but not debulking, is associated with a significant OS and DSS benefit even in systemically metastasized disease.

Keywords ATC · Anaplastic thyroid carcinoma · Thyroidectomy · Surgery · Survival

Introduction

Anaplastic thyroid carcinoma (ATC) is an orphan disease and one of the most aggressive cancers due to its rapid progression with limited mean survival of 3–6 months (Neff et al. 2008). Distant metastases that are often present at the time of initial diagnosis in ATC do not only result in a very dismal prognosis but also present a major challenge in decision making for the optimal treatment regime (Maso et al. 2017; Maniakas et al. 2020). At this stage most commonly utilized therapies include cytotoxic chemotherapy (ChT) with or without radiation therapy (RT) (Bible et al. 2021; Haddad et al. 2018; Filetti et al. 2019). More recently

✉ Lukas Käsmann
lukas.kaesmann@med.uni-muenchen.de

[1] Department of Radiation Oncology, University Hospital, LMU Munich, 81377 Munich, Germany

[2] Department of Internal Medicine IV, University Hospital, LMU Munich, 81377 Munich, Germany

[3] German Cancer Consortium (DKTK), Partner Site Munich, 80336 Munich, Germany

immunotherapeutic approaches and targeted therapies have been proposed for the treatment of advanced and metastatic ATC if targetable mutations are detected (Bible et al. 2021; Haddad et al. 2018; Filetti et al. 2019; Subbiah et al. 2018).

Current guidelines (National Comprehensive Cancer Network [NCCN], American Thyroid Association [ATA]) recommend to consider thyroidectomy also in ATC stage IVC if the primary tumor is considered resectable and R0/R1 margins are achievable (Bible et al. 2021; Haddad et al. 2018). It is important to consider local and distant complications when planning therapy at this stage of the disease and to evaluate individual susceptibility toward a chosen therapy within a multidisciplinary expert team. Surgical therapy to the primary tumor ranging from debulking surgery to R0 thyroidectomy could possibly prevent patients from developing life-threatening aspirations, dysphagia, dyspnea, bleedings or superior vena cava syndrome (Haigh et al. 2001). Some of these complications may, however, be prevented by less invasive interventions, e.g., tracheostomy, percutaneous endoscopic gastrostomy (PEG) or venous stenting. Furthermore, sufficient radiation therapy to the primary site or systemic therapies with platin-based agents or targeted therapies to actionable mutations such as *BRAF V600E*, or *NTRK* and *RET* gene fusions may also provide sufficient local control rates (Filetti et al. 2019). Thus, it is important to analyze outcomes and prognostic factors among patients with metastatic ATC to determine the rationale for an invasive intervention.

In this study we aim to investigate the role of different surgical procedures to the primary tumor in patients with ATC stage IVC on their survival. Hereby we compared various surgery types among each other by performing a systematic review of literature, pooled analysis derived from individualized patient data and SEER-database analysis.

Patients and methods

Systematic review of literature and pooled analysis

A systematic review of literature was primarily carried out on 30 th October 2020 and repeated on 15 August 2021

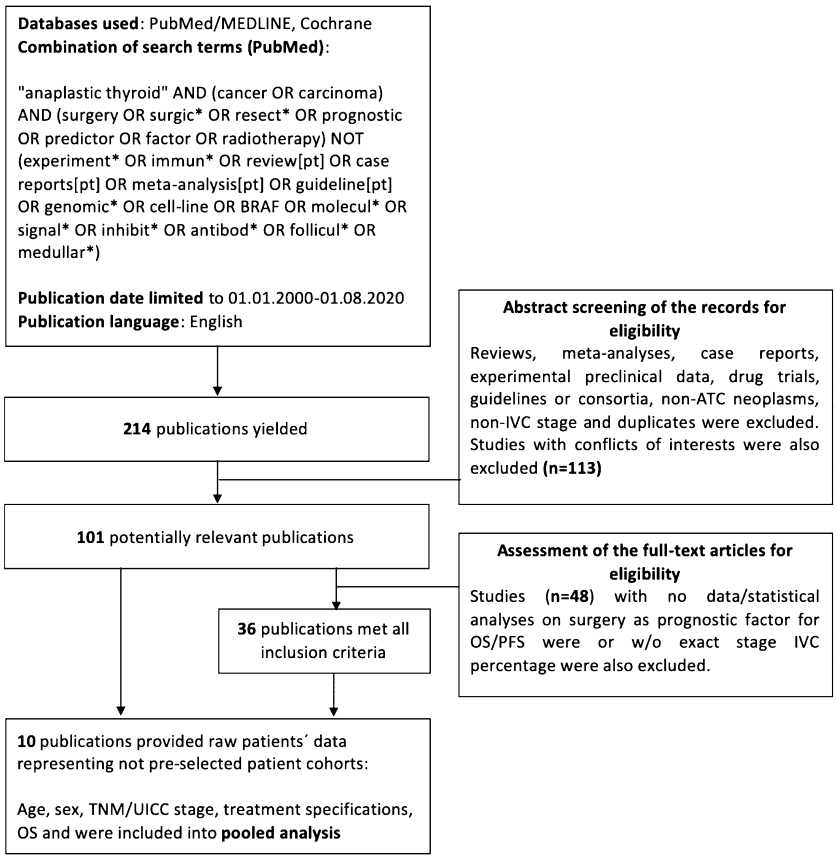


Fig. 1 PRISMA-flowchart for the systematic review of literature: surgery in stage IVC ATC patients

using PubMed/MEDLINE (National Center for Biotechnology Information, Bethesda, MD, USA) and Cochrane databases to identify relevant publications according to PRISMA-protocol. A full list of search terms is provided in Fig. 1. Articles published in English, in the timeframe from 1 January 2000 to 1 August 2021 and identified by the mentioned terms were included into the preliminary analysis. Further eligibility assessment incorporated abstract screening for article and neoplasm type, as well as duplicates. Studies with conflicts of interests, e.g. publications of our facility were excluded. Reviews, meta-analyses, case reports, experimental preclinical data, drug trials, guidelines or consortia and studies without stage IVC ATC were excluded. Remaining articles were analyzed in full-text and excluded, if data or statistical analyses on surgery as prognostic factor for OS/PFS were missing. Furthermore, only studies with exact stage IVC percentage data were included. Publications with individualized patients' data on age, sex, TNM/UICC stage, treatment specifications and OS were included into pooled analysis. The complete review process was based on the PRISMA guidelines and is depicted in Fig. 1.

A cohort of patients with metastatic ATC from our facility has been described previously and pooled with the newly identified data to form a representative cohort (Augustin et al. 2021). Inclusion and censorship criteria have been reported in that study.

SEER-based analysis

Based on the promising results of the pooled analysis we used Surveillance, Epidemiology, and End Results (SEER) database to further verify our null hypothesis. Data on all patients diagnosed with ATC employing histopathological codes of International Classification of Disease for Oncology (3rd edition; ICD-O-3; code 8021/3 [Carcinoma, anaplastic, NOS] and site [Thyroid]) from 2000 to 2016 were analyzed. Only patients with metastatic ATC were included into our study. Patients with aberrant stages as M1/IVC were excluded from the analysis. Staging was based on the SEER histological stage A (1973–2015) [Distant] and American Joint Committee on Cancer (AJCC) 3rd–7th editions [M1/IVC]. Following information was subsequently extracted from the SEER database: sex, age, surgery record and type according to "Rx Surg Prim Site (1998+)", RT codes and sequences, ChT records, cause-specific deaths codes, vital status and survival in months. Data acquisition date was 2 August 2021. Surgery records "isthmectomy only", "resection of less than one lobe" and "local surgical excision" were considered as debulking surgery. Patients without specified type of thyroidectomy "thyroidectomy NOS", "surgery NOS" or "unknown if surgery performed; death certificate ONLY" were excluded from the analysis.

Statistical analysis

Statistical analysis was conducted using SPSS statistics 25 (IBM, Chicago, IL, USA). Univariate analysis of variables comprised log-rank test. Significant variables were subsequently analyzed multivariately in the Cox regression. Significance level was defined for all analyses at $\alpha = 0.05$. In our single-center data patients were censored if lost to follow-up, overall survival (OS) was defined as the time from initial diagnosis to death, sufficient RT dose was defined as a total RT dose of ≥ 30 Gy due to a considerable number of patients receiving a total dose of < 30 Gy. In these cases, RT was mostly discontinued given the premature patients death or local complications.

Results

Systematic review of literature and pooled analysis

In total, 214 publications were yielded by our combination of search terms in the PubMed MEDLINE database. Cochrane search did not reveal any relevant studies. Potentially relevant publications accounted for 101 studies and were identified by abstract screening for eligibility, as shown in Fig. 1. Full-text assessment of these articles was based on the presence of statistical analyses specific for our hypothesis, namely, surgery as prognostic factor for improved overall or progression-free survival (OS, DSS and PFS, respectively). Thus, 36 retrospective studies were fully included into our systematic review (Table 1). A total of 12,725 patients were evaluated by the mentioned studies. Stage IVC accounted for 41.1% or approximately 5226 of these patients. Resection margins were reported at least partially by 16 (44.4%) of the studies. Twenty-seven (75%) publications showed surgery or certain resection status to be favorable for a longer survival, decreased relative risk or an improved local control (LC) in the univariate analysis. Two studies claimed their univariate analysis to be significant at α-levels of $p < 0.2$ or did not provide additional information on the significance level other than $p < 0.1$. In multivariate analysis, surgery or certain resection status were identified as an independent prognostic factor in 19 (52.7%) publications. Two publications did not provide p values for their multivariate analyses, but the 95% CI did not cross HR value of 1.0.

In total, 10 studies (Takahashi et al. 2019; Aslan et al. 2014; Crevoisier et al. 2004; Stavas et al. 2014; Ito et al. 2012; Lim et al. 2012; So et al. 2017; Tennvall et al. 2002; Troch et al. 2010; Busnardo et al. 2000) provided individualized patient data that were eligible for a pooled analysis with our single center cohort described previously (Augustin et al. 2021). This new cohort included 123 patients with stage IVC ATC and a median age of 71 (39–94) years

Table 1 Systematic review of literature—surgery in ATC

Author	Number of patients	Median age (IQR, years)	Stage IVA/IVB/IVC %	Surgery	R status	RT % and regimen	Total RT dose	ChT %	ChT agent	Additional information	Univariate for surgery (HR [95% CI]; *p* value)	Multivariate for surgery (HR [95% CI]; *p* value)
Fan et al. (2020)	104	63.5 (28–87)	4.8/73.1/22.1	NOS—50%	R0—12.5% R1—21.2% R2—16.3%	100.0	Median 66 Gy/33fr (6–70.25 Gy/3–40)	95.2—concurrent	DOX-based—73.7% PTX-based—24.3% Others—2%	Trimodal Therapy—51.0%	$p < .001$	0.278 [0.029–2.687]; $p = 0.269$. NS
Corrigan et al. (2019)	28	70.9 (63.8–74.7)	7.1/74.1/17.9	NOS 71.4%	NR	67.9	< 40 Gy—39.3% ≥ 40 Gy—21.4	50%	*With RT:* DOX—36.4% Other combinations—63.6%	S + RT + ChT—35.7% S + RT—17.9% RT + ChT—10.7% RT only—10.7% S only—17.9% ChT only—3.6%	0.384 (0.157–0.938), $p = .036$	0.198 (0.065–0.598), $p = .004$
Glaser et al. (2016)	3552	≥ 65—68.4%	NR/NR/41.6	TT—23.2% Other—26.3%	Margins negative—13.2% Margins positive/unknown—36.3%	58.7	Median 45 Gy (≤ 36 Gy—32.1%; ≥ 59.4 Gy—38.1%)	46.1	Single agent—57% Multiagent—43%	NR	S other than total: 1.32 (1.13–1.54), $p < 0.005$	OR for death within 2 y: 0.59 (95%CI 0.45–0.78), $p < 0.005$
Paunovic et al. (2015)	150	< 40—1.3 41–50—6.1 51–60—19.3 61–70—54.0 > 70—19.3	NR/NR/32.9	Tumor reduction—31.8 Lobectomy—4.7 Thyroidectomy and dissection—47.1	NR	81.2	NR	2.4	NR	NeoAd RT—2.4 Adj RT—78.8	RR 1.51 (1.30–1.81), $p < .001$	RR 0.43 (0.29–0.63) $p < .001$
Takahashi et al. (2019)	33	68 (41–87)	12/39/39	NOS—39%	NR	100	Median 50 Gy (5–74 Gy)	52	CARB + PTX—35.3% NDP + 5-FU—17.6% NDP + ETOP—11.8% PTX—11.8% Other—23.5% N = 17	CRT—45% N = 33	NS OS: 0.77 (0.35–1.66), $p = .510$ LC: 0.63 (0.18–2.07), $p = .445$	NR
Wendler et al. (2016)	100	70.5 (38–92)	9/32/54	Primary—83%: - TT—43% - HT—19% - Two-stage thyroidectomy—8% Tumor reduction—3%	R0—14% R1—27% R2—52%	83	Median 57.6 (13.5–80) Gy	56	DOX—25 PTX—9 PTX + PEM—8 DOX + CDDP—8 CARB + PTX—14 TKI´s—10 Other—10 (*absolute numbers as in the study*)	S + ChT + EBRT—49% S + EBRT—19% S only—11% EBRT only—9% EBRT + ChT—4% S + ChT—4% ChT only—0% Best supportive care—4%	NS, $p = .376$	NR
Jacobsen et al. (2017)	31	69 (26–87)	6.5/64.5/29	Any S—100% Thyroidectomy—69.2%	R0—38.5% R1—46.15% R2—15.4%	100	Median 64 (41.6–64) Gy	74.2	DOX-based—74.2%	RT Only—19.3% CRT—38.7% S + RT—6.5% S + CRT—35.5%	No S: 4.95 (2.01–12.2), $p < .2$	No S: 4.78 (1.92–11.9), $p < .2$

Table 1 (continued)

Author	Number of patients	Median age (IQR, years)	Stage IVA/IVB/IVC %	Surgery	R status	RT % and regimen	Total RT dose	ChT %	ChT agent	Additional information	Univariate for surgery (HR [95% CI]; *p* value)	Multivariate for surgery (HR [95% CI]; *p* value)
Bhatia et al. (2009)	53	Median NR; Mean: 66.1 ± 12.0	NR/NR/47.2	Complete—35.8% Subtotal—22.6%	NR	100	3DRT: 46.5 (4.0–70.0) Gy IMRT: 60.0 (39.9–69.0) Gy	91 (81% concurrent)	CARB/PTX—18.8% DOX/CDDP—16.7% CDDP—14.6% CARB—10.4% CDDP/ FLD/ARA-C—4.2% DOX/CDDP/ PTX—4.2% Other combinations—12.5%	NR	NS 0.57 (0.31–1.05), $p = .07$	NR
Kim et al. (2007)	121	Median NR; Mean: 64 ± 11	NR/NR/24	Bilateral—59% Unilateral—12%	NR	RT only—45.5 CRT—13.2	NR	20.7%	DOX + CDDP—88% GEM—8% DOX—4%	RT only—10.7% ChT only—1.6% ChT + RT—4.1% S only—20.7% S + RT—34.7% S + ChT—5.9% S + ChT + RT—9.1% BSC—13.2%	$p < .001$	NS
Brignardello et al. (2014)	55	73.15 (61.61–79.19)	0/43.6/56.4	74.5%: maximal debulking—70.1% Partial debulking—29.3%	NR	54.5	50–54 Gy in 1.8–2.0 Gy/fr	87.3	DOX and CDDP-based—87.5% PTX-based—12.5%	Early S alone—12.2% S + ChT—29.3% S + ChT + RT—58.5% NeoChT + RT + S—9.8% NeoChT + RT—4.9% NeoChT only—14.6%	Partial S: 5.33 (2.33–12.19), $p < .001$	Partial S: 5.36 (2.34–12.30), $p < .001$
Pezzi et al. (2017)	1288	Median NR; Mean—70.2	NR/NR/47	Any S—11.7%	NR	47.7	< 45 Gy—47.9% 45–59.9 Gy—21.8% 60–75 Gy—29.0% NR—1.3%	36.6	NR	NR	$p = .004$	0.786 (0.643–0.962), $p < .001$
Liu et al. (2016)	50	≤ 60—52% > 60—48%	30/38/32	100%	R0—34% R1—42% Other—24%	32	30–70 Gy—100% > 40 Gy—93.8%	16	IFX, DOX, DTIC	S only—42% S + RT/ChT—34% CRT—2% ChT only—4% Tracheostomy, biopsy, other—18%	R0&R1 vs. No S in ATC IVA/B: $p < .001$ S vs. non-S-treatment in ATC IVC: $p = .521$	S in ATC IVA/B: Exp(B) = .331, $p = .038$
Pierie et al. (2002)	67	73 (40–92)	NR/NR/49	Any S—65.7%: Complete—27.3% Incomplete—72.7%	NR	83.5	25–73 Gy: ≤ 45 Gy—51.8% > 45 Gy—48.2%	31.3	DOX-based—NR	NR	No S: 28.9 (CI—NR), $p < .0001$	Any S: 0.28 (CI—NR), $p = .0004$

Table 1 (continued)

Author	Number of patients	Median age (IQR, years)	Stage IVA/IVB/IVC %	Surgery	R status	RT % and regimen	Total RT dose	ChT %	ChT agent	Additional information	Univariate for surgery (HR [95% CI]; *p* value)	Multivariate for surgery (HR [95% CI]; *p* value)
Aslan et al. (2014)	29	64.5 (35–91)	10.3/62.1/27.6	Any S—55.2%: Total thyroidectomy—56.3% Subtotal—25% Biopsy—18.7%	R0—25% R1—25% R2—50%	65.5	NR	44.8	DOX—84.6% DOX + CDDP—7.7% (1) DOX + SOR—7.7% (1)	S + RT + ChT—31% S + RT—17.2% RT + ChT—13.8% RT only—3.5% (1) S only—10.3% None—24.1%	R0: $p = .05$	NR
Kihara et al. (2004)	19	Median NR; Mean: 73.4 (45–87)	NR/NR/47	Any S—53%: Complete—40%	R0—40% R1/2—NR	68.4	≥ 45 Gy—69.2% < 45 Gy—30.8%	63.2	DOX (alone/combination)—75% PTX—8.3% (1) Other—NR	S + RT + ChT—26.3% S + RT/ChT—10.5% S alone—15.8% Other—NR	Complete/no S: $p = .002$	Incomplete resection: RR 1.475 (1.168–16.340), $p = .0284$
Zivaljevic et al. (2014)	150	Median NR; (35–89) ≤ 60—26.7% > 60—73.3%	NR/NR/32.9	Any S—56.7%: Lobectomy—4.7% Thyroidectomy and dissection—47.1% Tumor reduction—31.8% Biopsy—14.1% Tracheotomy—2.4%	NR	Pre/Post S: 46	NR	1.3%	NR	NR	$p < .1$	OR = 0.43 (0.29–0.63), p < .001
Huang et al. (2019)	735	70 (60–80)	NR/NR/44.1	Any S—44.2%: TT—60% Less than TT—40%	NR	54.7	NR	42.4	NR	No treatment—21.9% ChT only—3.7% S only—16.3% S + ChT—2.6% RT only—11% RT + ChT—17.2% S + RT—7.7% S + RT + ChT—19.5% Total: 725 patients (Table 2)	$p < .001$	TT vs. Less than TT: 0.655 (0.521–0.838), $p = .001$)
Yau et al. (2008)	50	72 (36–104)	NR/NR/18	Any S—68%: TT—82.4% Subtotal—8.8% Lobectomy—5.9% Radiofrequency ablation—2.9% (1)	NR	46	NR	36	NR	NR	$p < .01$	NS
Sun et al. (2015)	42	60 (42–80)	7.1/69.1/23.8	Any S—78.6%: Thyroidectomy alone—60.1% Thyroidectomy + neck dissection—38.9%	NR	100	24–70 Gy < 40 Gy—47.6% ≥ 40 Gy—52.4%	28.6	DOX + CDDP—25% PTX + CDDP—33.3% BLEO, 5-FU + CDDP—41.7%	ChT alone—4.8% S alone—11.9% RT alone—28.6% S + RT—26.2% S + RT + ChT—14.3% S + ChT—9.5% No treatment—4.8%	3-year OS for S type: $p = .113$	NR

Table 1 (continued)

Author	Number of patients	Median age (IQR, years)	Stage IVA/IVB/IVC %	Surgery	R status	RT % and regimen	Total RT dose	ChT %	ChT agent	Additional information	Univariate for surgery (HR [95% CI]; *p* value)	Multivariate for surgery (HR [95% CI]; *p* value)
Lee et al. (2016b)	98	Median NR; 63.5–13.4	NR/NR/20.4	NOS—58.2%	NR	17.3	NR	7.1	NR	NR	Resectability: OR: 2.57 (1.60–4.15), $p < .001$	Resectability: Adjusted OR: 1.39 (1.21–1.74), $p = .004$
Haigh et al. (2001)	33	69 (47–80)	NR/NR/64	Any S—79%: TT—54% Near-total thyroidectomy—19% Total thyroid lobectomy—12% Minor excision/isthmusectomy—8% Node dissection alone—8% Concomitant neck dissection—31% Concomitant tracheostomy—8%	NR	NR	45–75 Gy	NR	DOX, PTX, CDDP, CARB, ETOP, CYC, MEL, BLEO	NR	Curative S vs. Palliative S: $p < .001$	Curative S: RR 0.1 (0.02–0.63), $p = .01$
Baek et al. (2017)	329	Median NR; 68.1 (22–89)	17.3/49.5/31.3	Any S—57.1%: Curative S—50% Curative S + CRT/RT—44.7% Curative S + ChT—5.3%	R0—11.7% R1—71.3% NR—17%	40.7	< 40 Gy—24.6% ≥ 40 Gy—75.4%	NR	CDDP, CARB, DTX, PTX, DOX	No definite treatment—24.6% RT/concurrent CRT—15.2% Curative resection—28.6% Curative resection and adjuvant RT/concurrent CRT—25.5% Curative resection and adjuvant chemotherapy—3% Chemotherapy—3%	Treatment method including S: $p < .01$	Curative S only: 0.505 (0.339–0.752), $p < .01$
Dumke et al. (2014)	40	67 (38–84)	NR/NR/22.5 (at diagnosis)	Any S—80%: TT—68% Subtotal—12%	R0—10% R1—7.5% R2—50% Rx—32.5%	97.5	Median 50 (6–60.4) Gy	15	Mono DOX—2patients PTX mono/ combination IFX/ CARB/ ETOP, EPR mono + unknown protocol—á 1 patient	NR	R-status: $p = .41$	NR

Table 1 (continued)

Author	Number of patients	Median age (IQR, years)	Stage IVA/IVB/IVC %	Surgery	R status	RT % and regimen	Total RT dose	ChT %	ChT agent	Additional information	Univariate for surgery (HR [95% CI]; *p* value)	Multivariate for surgery (HR [95% CI]; *p* value)
Mohebati et al. (2014)	83	60 (28–89)	NR/NR/24	NOS—83%	R0/1—40.6% R2/x—59.4%	assured 64	6–70 Gy	assured 57	DOX ± Pt-based ChT	S ± RT ± ChT—71% S alone—12% ChT/RT—5% RT alone—4% S + RT—14% S + PORT + ChT—46% S + ChT—11%	$p < .001$	2996 (1.2–7.1), $p = .013$
Kebebew et al. (2005)	516	Median NR; Mean 71.3 ± 12.7	NR/NR/43	Any S—49%: Total—4.7% Subtotal or near TT—14.6% Lobectomy and/or isthmusectomy—9.1% Removal < lobe—3.2% Thyroidectomy, NOS—2 p Surgery, NOS—67.6%	NR	63.2	NR	NR	NR	NR	$p < .0001$	NS 0.779 (0.312–1.946)
Akaishi et al. (2011)	100	68 (41–90)	11/31/58	Any S—70%: TT—50% Subtotal—15.7% Lobectomy—32.9% Partial lobectomy—1.4% (1)	R0—34.3% R1/2—65.7%	78	≥ 40 Gy—74.4% < 40 Gy—25.6%	28	PTX, CDDP, DOX, ETOP-based	S + CRT—15% S + RT—60% CRT—5% RT alone—10% ChT alone—10%	$p < .0001$	No S: RR 3.99 (2.37–6.66), $p < .0001$
Derbel et al. (2011)	44	65 (44–80)	NR/NR/45.4	Any S—100%: TT—63.6% Near total thyroidectomy—15.9% Biopsy/Debulking—20.4%	NR	88.5	46–50 Gy	86.4	DOX + CDDP—86.8% DOX + CARB—7.9% DOX—2.6% (1) PTX—2.6% (1)	S alone—4.5% S + ChT—7% S + RT + ChT—79.5% RT alone—4.5% S + RT—4.5%	Near-total/total S: $p < .05$	NR
Crevoisier et al. (2004)	30	Median NR; Mean 59 (40–79)	NR/NR/20	Any S—80%	MCR—58.3% IR—41.7%	100	40–55 Gy	100	DOX (60 mg/m2) + CDDP (120 mg/m2)—100%	NR	$p = .01$	MCR: 2.7 (1.1–6.8), $p = .04$
Haymart et al. (2013)	2742	Mean: 70 ± 12.29	37.6/37.3/25.1 (n = 649)	Any S—51.4% ($n = 2086$): Total thyroidectomy—64% Lobectomy—26%	NR	60.4 (n = 2086)	NR	40% (n = 2086)	NR	NR	$p < .001$	No S: UHR 1.85 (1.67, 2.05) AHR 1.79 (1.61, 1.99)
McIver et al. (2001)	134	Mean: 60	NR/NR/46	Any S—72%: TT—13% Near-total—29% Lobectomy—46% Complex—12%	Complete—30% Minimal residue—26% Gross incomplete—44%	50	NR	12	NR	S + RT—39.6% S + ChT—9.4%	NS $p > .4$	NR

Table 1 (continued)

Author	Number of patients	Median age (IQR, years)	Stage IVA/IVB/IVC %	Surgery	R status	RT % and regimen	Total RT dose	ChT %	ChT agent	Additional information	Univariate for surgery (HR [95% CI]; *p* value)	Multivariate for surgery (HR [95% CI]; *p* value)
Sugitani et al. (2012)	677 (547 with common type ATC)	Mean: 68.7 ± 11.0	13/44/42	Any S—55%: Palliative—51.8% Radical—48.2%	NR	58.3	< 40 Gy—75.2% ≥ 40 Gy—24.6%	46.6	NR	NR	*p* = .0002	Radical S: 0.43 (0.27–0.68), *p* = 0003
Brignardello et al. (2007)	27	46–92	NR/NR/55.6	Any S—74.1%:Maximal debulking—70% Palliative—30%	NR	55.6	36–40 Gy	55.6	DOX, CDDP, PTX	NR	Maximal debulking: 0.18 (0.06–0.54)	Maximal debulking: 0.23 (0.07–0.79)
Ridder et al. (2020)	812	73 (29–99)	NR/NR/42.1	NOS—31%	NR	52	NR	11	NR	Only S/RT/ChT—40% S + RT/CRT/S + ChT/RT + ChT—20% S + CRT/S + RT + ChT—4%	0.4 (0.3–0.5), *p* < .001	0.5 (0.4–0.6), *p* < .001
Roche et al. (2010)	26	Mean 72.1 (52.3–90.8)	NR/NR/15.4	Any S—84.6%: TT/subtotal—72.7% Lobo-isthmectomies/hemithyroidectomies—18.2% Tumorectomy—9.1%	R0—46.2% R1—53.9% (*n* = 26)	53.8	NR	19.2	NR	Adjuvant RT—50% S + RT + ChT—19.2%	R0/R1 *p* = .014	NS
Gui et al. (2020)	1014	≥ 65—64.5% < 65—35.5%	NR/NR/56.1	Any S—45.5%: TT—61.9% Lobectomy—38.1%	NR	56.3	NR	NR	NR	NR	Total: 0.705 (0.570–0.873), *p* = .001	Total: 0.782 (0.630–0.971), *p* = .026
Ito et al. (2012)	40	74 (52–85)	0/62.5/37.5	Any S—50% TT—40% Subtotal/near-total—20% Palliative/tracheostomy—40%	R0—0% R1—10% R2—90%	70	45–60 Gy	52.5	Combinations of CDDP, ADM, EPR, ETOP, DTX, 5-FU and PTX	NR	S + CRT beneficial for median survival time: *p* < .01	NR

S surgery, *ChT* chemotherapy, *RT* radiation therapy, *CRT* concurrent chemoradiotherapy, *TT* total thyroidectomy, *HT* hemithyroidectomy, *NOS* not otherwise specified, *NR* not reported, *R* resection status, *IQR* interquartile range, *HR* hazard ratio, *RR* relative risk, *OR* Odds ratio, *CI* confidence interval, *OS* overall survival, *LC* local control, *EBRT* external beam radiation therapy, *NeoAd* neoadjuvant, *Adj* adjuvant, *fr.* fraction, *Gy* Gray, *DOX* doxorubicine, *PTX* paclitaxel, *CARB* carboplatin, *NDP* nedaplatin, *5-FU* 5-fluoruracil, *ETOP* etoposide, *PEM* pemetrexed, *CDDP* cisplatin, *TKI* tyrosine kinase inhibitor, *FLD* fludarabine, *ARA-C* cytarabine, *CYC* cyclophosphamide, *MEL* melphalan, *BLEO* bleomycin, *SOR* sorafenib, *DTIC* dacarbazine, *IFX* ifosfamide, *GEM* gemcitabine

Table 2 Patients characteristics from the pooled analysis: whole cohort and only operated patients

Characteristic	Number and %	Number and %
Age in years (median, IQR)	71 (39–97)	68 (39–83)
	$n=123$	$n=39$
Age group		
< 50 years	5 (4.1%)	3 (7.7%)
50–59 years	19 (15.4%)	6 (15.4%)
60–69 years	28 (22.8%)	11 (28.2%)
70–79 years	50 (40.7%)	18 (46.2%)
≥ 80 years	21 (17.1%)	1 (2.6%)
Elderly patients		
≥ 65 years	40 (67.5%)	24 (61.5%)
< 65 years	83 (32.5%)	15 (38.5%)
Sex		
Female	71 (57.7%)	22 (56.4%)
Male	44 (35.8%)	15 (38.5%)
Not reported	8 (6.5%)	2 (5.1%)
	$n=123$	$n=39$
Stage		
IVC	100%	100%
ChT record	76 (61.8%)	33 (84.6%)
RT/ChT sequence		
ChT concurrent to RT	49 (39.8%)	23 (39.8%)
ChT not concurrent to RT	11 (8.9%)	6 (8.9%)
ChT without RT ± surgery	12 (9.8%)	2 (9.8%)
RT without ChT ± surgery	29 (23.6%)	4 (23.6%)
No ChT and no RT ± surgery	18 (14.6%)	2 (14.6%)
Sequence unknown	4 (3.3%)	2 (3.3%)
RT record	97 (76.4%)	35 (89.7%)
Sufficient RT ≥ 30 Gy	80 (*82.5%)	33 (*94.3%)
RT dose unknown	2 (*2.1%),	1 (*2.85%),
	*$n=97$	*$n=35$
Surgery	39 (31.7%)	39 (100%)
Surgery type	$n=39$	–
Total thyroidectomy	11 (28.2%)	
Subtotal OR near-total thyroidectomy	4 (10.3%)	
Lobectomy/hemi-thyroidectomy	2 (5.1%)	
Debulking	5 (12.8%)	
N/A	17 (43.6%)	
Resection margins	$n=39$	–
R0	2 (5.1%)	
R1	17 (43.6%)	
R2	16 (41.0%)	
N/A	4 (10.3)	
Margins < R2	$n=39$	–
Yes	16 (41.0%)	
No	19 (48.7%)	
N/A	4 (10.3%)	
Multimodal treatment	21 (17.1%)	21 (53.8%)
Total number of patients	123	39

(Table 2). Treatment records were available for RT, ChT and surgery in 61.8, 76.4 and 31.7% of the cases, respectively. Treatment sequences with RT/ChT were reported for 96.7% of the population. In 39.8% of the cases, concurrent chemoradiotherapy (CRT) was administered. Sufficient RT was used in 33 (26.8%) cases. Surgical intervention included debulking, sub- or near total thyroidectomy, total thyroidectomy or was not specified. Information about resection status was available for 35 (28.4%) of these patients and multimodal treatment was applied in 21 (17.1%) of the cases. OS rate was 27.1% and 7.9% at 6 and 12 months, respectively. In the univariate analysis surgery ($p<0.001$), administration of sufficient RT ≥ 30 Gy ($p<0.001$), ChT ($p<0.001$) and multimodal treatment ($p=0.014$) resulted in improved OS (Fig. 2A–D). A specific age group or the age < 65 years did not correlate with an improved OS, but there was a tendency for patients < 65 years towards a better survival rate at 6 months: 19.3 vs. 27.1%. In the multivariate analysis, only surgery (1.997 [1.162–3.433], $p=0.012$) and sufficient RT ≥ 30 Gy (1.877 [1.232–2.843], $p=0.012$) were identified as independent predictors for OS (Table 3).

To identify the most favorable surgical approach, we selected or identified patients with ATC stage IVC who underwent different surgical procedures, and analyzed possible predictors for an improved OS. A sub-cohort of 39 patients was investigated (Table 2). Median age was 68 (39–83) years, 84.6% of the patients received RT ≥ 30 Gy, 39.8%—with concurrent ChT, and multimodal therapy was administered to 53.8%. Surgical types analyzed included total thyroidectomy in 28.2% of the cases, sub- or near total thyroidectomy, lobectomy/hemi-thyroidectomy and debulking in 10.3, 5.1 and 12.8% of the cases, respectively. Surgical data of 43.6% of the operated patients was, unfortunately, not available. Resection margins other than R2 were reported for 41% of the patients. In the univariate analysis only, total thyroidectomy showed a tendency towards an improved OS, when compared to other surgery types with survival rates at 9 months of 45 and 30%, respectively ($p=0.058$) (Fig. 3A, B). Margin status, therapy regimen, age or multimodality were not significantly correlating with OS in the operated sub-cohort.

Given the insufficiency of the individual surgical data gathered from the pooled analysis we decided to use SEER data base to identify best surgical approach. Therefore, we have analyzed a cohort of 617 ATC stage IVC patients (Table 4). Median age was 69 (33–97) years, ChT and RT were employed in 61.4 and 52% of patients, respectively. A total of 187 (30.3%) patients underwent surgery, i.e., either lobectomy and/or isthmectomy, removal of less than one lobe, sub- or near-total thyroidectomy and total thyroidectomy in 22.4, 18.2, 11.8 and 47.6% of cases, respectively. Multimodal treatment was administered to a total of 11.7% of patients and > 75% of all patients had an ATC-related

Journal of Cancer Research and Clinical Oncology (2023) 149:3527–3547 3537

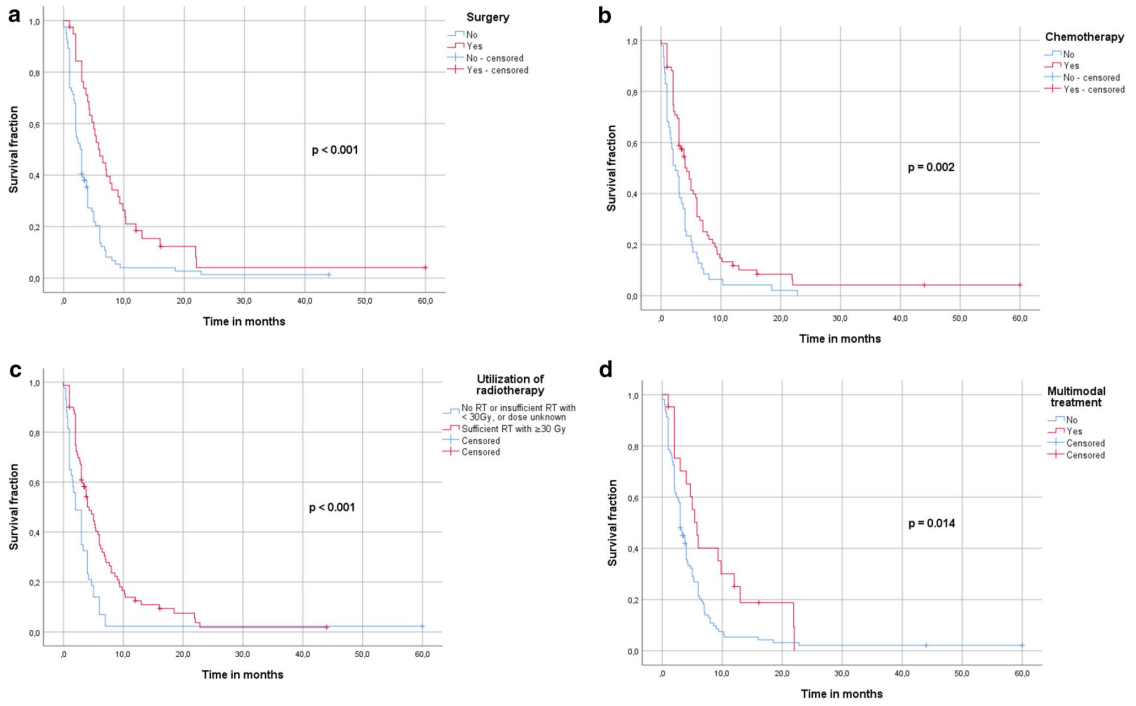


Fig. 2 **A**–**D**. Univariate analysis of prognostic factors for patients from the pooled cohort

Table 3 Uni- and multivariate analyses of the pooled cohort

Cohort	Univariate analysis	Multivariate analysis (HR, 95%CI, *p* value)
Total	–	–
Surgery	***p* < 0.001**	**1.997 [1.162–3.433], *p* = 0.012**
ChT record	***p* = 0.002**	1.479 [0.982–2.228], *p* = 0.061
Sufficient RT ≥ 30 Gy vs. No RT/ RT < 30 Gy/dose NA	***p* < 0.001**	**1.877 [1.232–2.843], *p* = 0.012**
Multimodal treatment with RT ≥ 30 Gy	***p* = 0.014**	0.772 [0.384–1.555], *p* = 0.469
Age cohorts	*p* = 0.844	–
Elderly (≥ 65 years)	*p* = 0.65	–

Statistically significant values ($p < 0.05$) are in bold

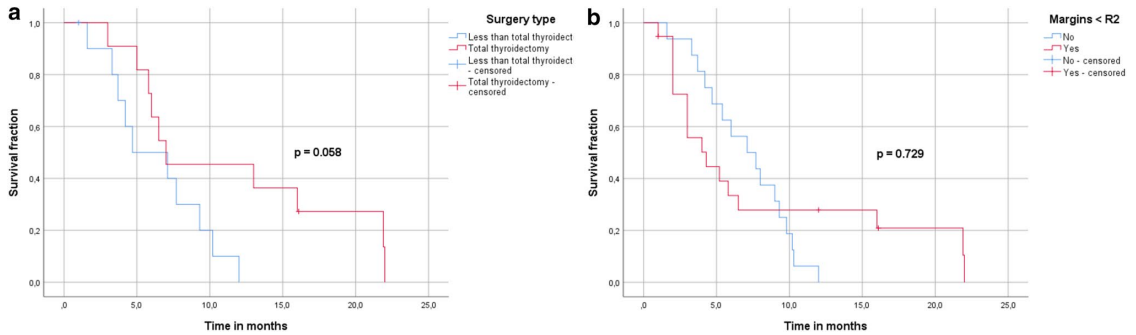


Fig. 3 **A**–**B**. Univariate analysis of prognostic factors within the operated cohort from the pooled analysis

Table 4 Patient characteristics from SEER database (any treatment left, without best supportive care mid, operated right)

Characteristic	Number and %	Number and %	Number and %
Age in years (median, IQR)	69 (33–97)	67 (34–93)	66 (34–93)
Age group			
< 50 years	44 (7.1%)	40 (9.0%)	22 (11.8%)
50–59 years	95 (15.4%)	78 (17.5%)	34 (18.2%)
60–69 years	176 (28.5%)	134 (30.1%)	61 (32.6%)
70–79 years	169 (27.4%)	117 (26.3%)	47 (25.1%)
≥ 80 years	133 (21.6%)	76 (17.1%)	23 (12.3%)
Elderly patients			
≥ 65 years	393 (67.3%)	188 (42.2%)	87 (46.5%)
< 65 years	224 (36.3%)	257 (57.8%)	100 (53.5%)
Sex			
Female	346 (56.1%)	225 (50.6%)	87 (46.5%)
Male	271 (43.9%)	220 (49.4%)	100 (53.5%)
Years of diagnosis			
2000–2004	129 (20.9%)	97 (21.8%)	34 (18.2%)
2005–2010	206 (33.4%)	148 (33.3%)	64 (34.2%)
2011–2016	282 (45.7%)	200 (44.9%)	89 (47.6%)
ChT	238 (38.5%)	238 (53.5%)	88 (47.1%)
RT record	321 (52.0%)	321 (72.3%)	103 (55.1%)
RT sequence	$n = 617$	$n = 445$	$n = 187$
No RT AND/OR cancer-directed surgery	486 (78.8%)	314 (70.6%)	84 (44.9%)
Adjuvant	123 (19.9%)	123 (27.6%)	98 (53.4%)
Neoadjuvant	3 (0.5%)	3 (0.7%)	2 (1.1%)
Before AND after surgery	5 (0.8%)	5 (1.1%)	3 (1.6%)
Surgery	187 (30.3%)	187 (42%)	187 (100%)
Surgery type	$n = 187$	–	–
Lobectomy AND/OR isthmectomy	42 (22.4%)		
Removal of less than one lobe, NOS	34 (18.2%)		
Subtotal OR near-total thyroidectomy	22 (11.8%)		
Total thyroidectomy	89 (47.6%)		
Multimodal treatment	72 (11.7%)	72 (16.2%)	72 (38.5%)
Cause of death			
N/A not first tumor	94 (15.2%)	59 (13.3%)	31 (16.6%)
Dead, attributable to ATC	472 (76.5%)	346 (78.8%)	133 (71.1%)
Alive OR dead of other cause	44 (7.1%)	35 (7.9%)	21 (11.2%)
Dead, but COD missing/unknown	7 (1.1%)	5 (1.1%)	2 (1.1%)
Total number of patients	617	445	187

death. On the univariate analysis surgery ($p < 0.001$), administration of ChT ($p < 0.001$) or RT($p < 0.001$), multimodal treatment ($p < 0.001$) and age group ($p < 0.001$) correlated with an improved OS and DSS. Age ≥ 65 years (OS: $p < 0.001$, DSS: $p = 0.008$) correlated with a worsened OS and DSS (Suppl. Figures 1A–F, 2A–F). On the multivariate analysis surgery (OS–HR 1.934, 95% CI 1.538–2.427, $p < 0.001$; DSS–HR 1.803, 95% CI 1.275–2.550, $p < 0.001$), RT (OS–HR 1.873, 95% CI 1.558–2.247, $p < 0.001$; DSS–HR 1.611, 95% CI 1.191–2.178, $p = 0.002$), ChT (HR 1.727, 95% CI 1.412–2.114, $p < 0.001$; DSS–HR 1.572, 95% CI 1.197–2.064, $p = 0.001$) were independent predictors for an improved OS and DSS (Table 5). Age ≥ 65 years (HR 0.795, 95% CI 0.665–0.950, $p = 0.012$) was also identified as an independent predictor for a higher overall mortality. Administration of best supportive care only correlated inversely with DSS on the univariate analysis ($p < 0.001$), but it was not an independent predictor for a worse DSS.

Furthermore, we eliminated 172 patients from our analysis, who did not receive any cancer-directed treatment, to verify predictors for an improved OS/DSS. On the univariate analysis surgery ($p < 0.001$), RT ($p < 0.001$), ChT ($p < 0.001$), multimodal treatment ($p < 0.001$), age ≥ 65 years ($p < 0.001$) and combinations of therapies (not trimodal) vs. RT alone

Table 5 Multivariate analysis of prognostic factors for OS and DSS of the SEER cohorts

Factor	Whole cohort						Without BSC					
	OS			DSS			OS			DSS		
	HR	95%CI	*p* value	HR	95%CI	*p* value	HR	95%CI	*p* value	HR	95%CI	*p* value
Surgery	1.953	1.557–2.450	**< 0.001**	1.803	1.275–2.550	**< 0.001**	1.769	1.289–2.427	**< 0.001**	1.913	1.286–2.845	**0.001***
RT	1.880	1.566–2.258	**< 0.001**	1.611	1.191–2.178	**0.002***	1.729	1.311–2.280	**< 0.001**	1.490	1.058–2.099	**0.022***
ChT	1.723	1.409–2.108	**< 0.001**	1.572	1.197–2.064	**0.001***	1.638	1.273–2.106	**< 0.001**	1.579	1.203–2.072	**< 0.001**
Multimodal treatment	0.692	0.478–1.002	0.051	0.900	0.542–1.494	0.683	0.790	0.499–1.249	0.313	0.844	0.504–1.413	0.518
Age ≥ 65 years	0.795	0.665–0.950	**0.012**	0.970	0.799–1.178	0.760	0.789	0.644–0.967	**0.022**	NA	NA	NA

Statistically significant values ($p < 0.05$) are in bold

($p < 0.001$) or surgery alone ($p < 0.001$), correlated with an improved OS (Suppl. Figure 3A–E). Multivariately, surgery (HR 1.769, 95% CI 1.289–2.427, $p < 0.001$) administration of RT (HR 1.729, 95% CI 1.311–2.280, $p < 0.001$), ChT (HR 1.638, 95% CI 1.273–2.106, $p < 0.001$) and age <65 years (HR 0.789, 95% CI 0.644–0.967, $p = 0.022$) were independent predictors for an improved OS (Table 5). Univariate analyses for DSS showed similar correlations: surgery ($p < 0.001$), ChT ($p < 0.001$), RT ($p = 0.002$), multimodal treatment ($p < 0.001$), ChT without RT or without surgery vs. surgery and RT ± ChT ($p < 0.001$), combined therapies (not only trimodal) vs. RT only ($p < 0.001$) or surgery only ($p = 0.008$) (Fig. 4A–E). On the multivariate analysis surgery (HR 1.913, 95% CI 1.286–2.845, $p = 0.001$) administration of RT (HR 1.490, 95% CI 1.058–2.099, $p = 0.022$) and ChT (HR 1.579, 95% CI 1.203–2.072, $p < 0.001$) were independent predictors for an improved DSS (Table 5).

To identify specific surgical interventions, that correlate with best OS/DSS, we subsequently analyzed a separate cohort of patients, who all underwent surgery and/or any other cancer-directed treatment. On the univariate analysis, total thyroidectomy ($p = 0.031$), administration of ChT ($p = 0.007$), RT ($p < 0.001$), combination of surgery and RT ± ChT ($p < 0.001$) and multimodal treatment ($p < 0.001$) correlated with an improved DSS (Fig. 5A–I). Debulking surgery inversely correlated with the DSS ($p < 0.001$) (Fig. 5D). On the multivariate analysis, debulking surgery was an independent predictor for a worse outcome (HR 0.535, 95% CI 0.332–0.862, $p = 0.010$), whereas RT administration correlated with a longer DSS (HR 2.316, 95% CI 1.362–3.939, $p = 0.002$) (Table 6). Total, sub-total and near-total thyroidectomy showed significantly longer DSS than other thyroid surgeries ($p = 0.043$ and $p = 0.031$) (Fig. 5A, B). On the other hand, if debulking patients were eliminated from the analysis, there was no significant difference in the DSS, when comparing total and less than total thyroidectomy (OS–$p = 0.115$; DSS–$p = 0.463$, Fig. 5C, Suppl. Figure 4C). Similarly, total thyroidectomy ($p = 0.005$), administration of ChT ($p < 0.001$), RT ($p < 0.001$), as well as multimodality ($p < 0.001$) and age <65 years ($p = 0.002$) correlated with a longer OS (Suppl. Figure 4A–I). However, on the multivariate analysis only administration of RT (HR 2.349, 95% CI 1.469–3.757, $p < 0.001$) and debulking (HR 1.564, 95% CI 1.024–2.389, $p = 0.038$) were independent predictors for OS (Table 6).

Discussion

In the current study, we have evaluated the impact of different thyroid surgical strategies on OS and DSS in 3 different cohorts of patients with ATC stage IVC and found it to be associated with a significantly improved outcome.

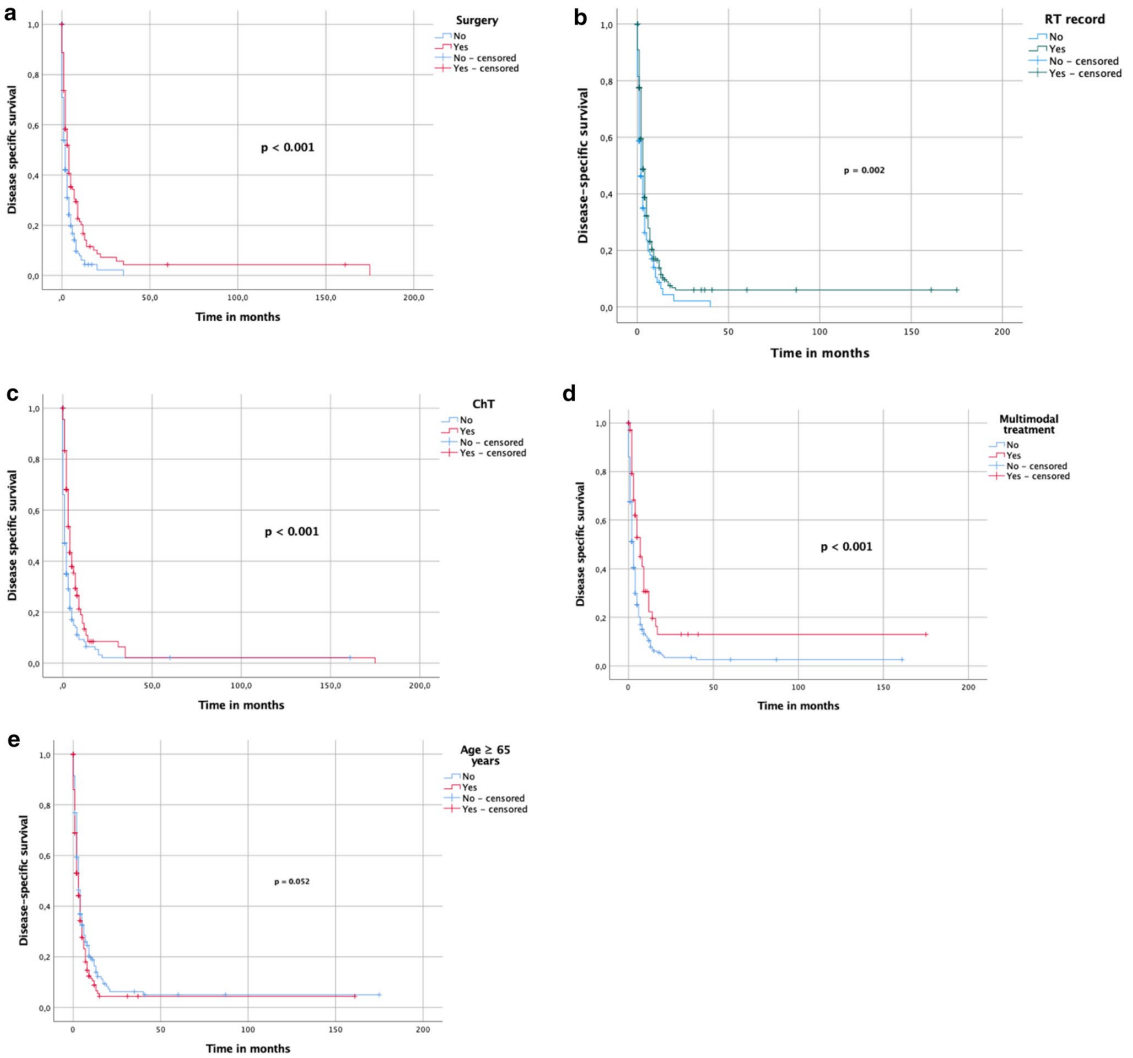


Fig. 4 **A**–**E**. DSS of patients from SEER database without best supportive care only regimen

Furthermore, we showed that administration of RT, ChT and multimodal therapy, as well as younger age correlate with an improved OS or DSS.

The role of surgical treatment in metastatic ATC remains controversial. There are several treatment approaches at this stage, which may include surgery to the primary tumor and neck dissection depending on the specific guideline (Bible et al. 2021; Haddad et al. 2018; Filetti et al. 2019). Oncological surgical approaches in ATC vary from total thyroidectomy, subtotal or near total thyroidectomy to debulking. On the basis of tumor size and/or infiltration of adjacent structures, as well as extent of metastatic disease, i.e., T-/N-/M-stage, different strategies have to be considered within a multidisciplinary board. Removal of one of the lobes is less invasive, but yet only plausible in patients with intrathyroidal or incidental ATC, whereas total thyroidectomy is recommended by most of the guidelines (Bible et al. 2021; Haddad et al. 2018; Smallridge et al. 2012). If feasible and the tumor classified as resectable, R0/R1 resection has to be goal (Haddad et al. 2018), which, however, is rarely achievable given the infiltrative growth pattern (Filetti et al. 2019). Based on our systematic review, several studies have reported a negative resection margin to be associated with a survival benefit (Aslan et al. 2014; Glaser et al. 2016; Roche

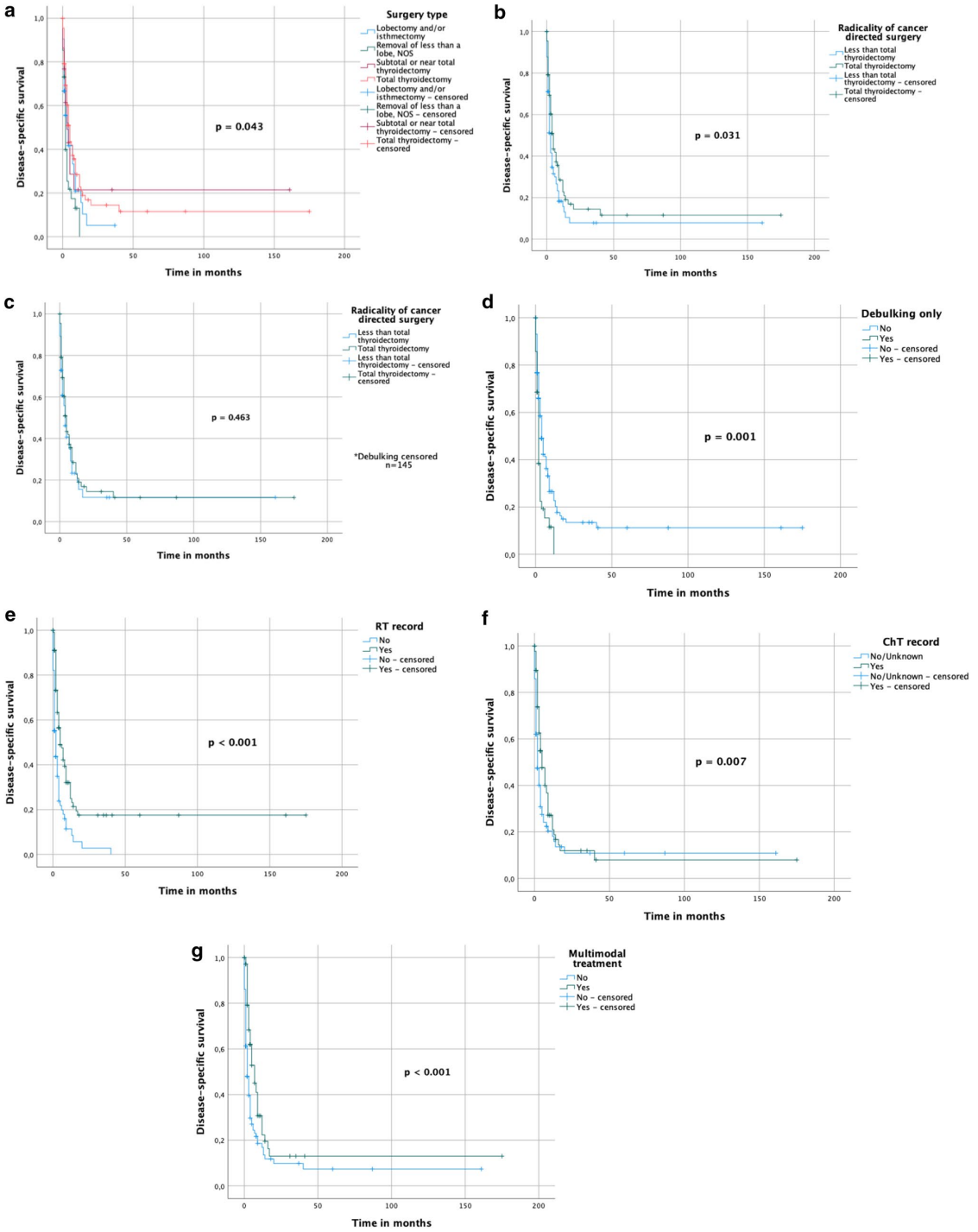


Fig. 5 **A**–**G**. DSS of operated patients from SEER database

Table 6 Multivariate analysis of prognostic factors for OS and DSS within the operated SEER cohort

Factor	OS			DSS		
	HR	95%CI	*p* value	HR	95%CI	*p* value
Radicality of cancer-directed surgery	0.851	0.593–1.220	0.38	0.908	0.605–1.364	0.643
Debulking only	1.564	1.024–2.389	**0.038**	0.535	0.332–0.862	**0.010**
ChT administrated	1.433	0.818–2.511	0.209	1.150	0.651–2.033	0.630
RT administrated	2.349	1.469–3.757	**< 0.001**	2.316	1.362–3.939	**0.002**
Multimodal treatment	0.711	0.345–1.469	0.357	0.937	0.430–2.039	0.869
Age ≥ 65 years	0.794	0.570–1.105	0.171	NA	NA	NA

Statistically significant values ($p < 0.05$) are in bold

et al. 2010; Liu et al. 2016; Passler et al. 1999). However, our pooled analysis on the resection status did not show any correlation with survival, which may be attributed to a small and heterogeneous sample size of only 35 patients with accurate data on the resection margins. Since ATC is characterized by an aggressive growth, it often infiltrates neighboring structures, so that an option of an ultra-radical resection including laryngectomy, resection of the infrahyoid muscles, trachea or esophagus arises. Thus, Sugitani et al. (Sugitani et al. 2014) found ultra-radical surgery to offer a benefit for survival in patients with an ATC IVB. Conversely, Goffredo et al. (Goffredo et al. 2015) evaluated a retrospective cohort of 335 operated ATC patients and did not find a survival benefit for aggressive resections in stages IVB and IVC. In that study a missing potential benefit from surgery was attributed to the morbidities and operative risks of radical resections. In our systematic review we did not find any of the studies evaluating exclusively ATC IVC patients or comparing radical resections with limited thyroid surgeries. However, some large-scale studies (Glaser et al. 2016; Sugitani et al. 2012; Gui et al. 2020; Ridder et al. 2020; Haymart et al. 2013; Kebebew et al. 2005; Huang et al. 2019; Pezzi et al. 2017) have reported their cohorts to contain up to 56.1% stage IVC patients and all of these studies found surgery to be associated with an improved OS (Gui et al. 2020). This is similar to our findings, that surgical treatment to the primary tumor also in an advanced stage ATC is an appropriate treatment option and can bear a significant survival benefit in selected patients. In addition, we have shown total thyroidectomy as a specified surgical approach to correlate with an improved OS/DSS. In that analysis we found no difference between TT and less than TT surgeries excluding debulking, i.e., compared subtotal-, near total thyroidectomies or lobectomies. This is in line with a study of Venkatesh et al. who reported less invasive thyroidectomies to be non-inferior to TT in terms of OS (Venkatesh et al. 1990). In our pooled analysis, we were only able to see a tendency regimen toward an improved OS for TT ($p = 0.058$).

Removal of the gross tumor in the head and neck region is of crucial importance for adjuvant RT or ChT, since it facilitates a beneficial local control by these therapies, as it was shown for ATC by some authors (Glaser et al. 2016; Fan et al. 2020). However, the extent of primary tumor-directed surgery needs to take into consideration the extent of primary tumor spread. The risk–benefit-ratio needs to be thoroughly evaluated between surgery to the primary tumor which may enhance therapeutic outcome and the risk of surgery-induced morbidity and delay of systemic therapy. The main goal of surgery to the primary tumor in systemically metastasized ATC is to avoid potential complications from the locally destructive tumor growth leading to obstructions of airway and hence respiratory insufficiency, as well as compression and/or infiltration of carotid vessels, as these are common death causes reported to date (Kitamura et al. 1999). Nilsson et al. investigated debulking surgery to the primary tumor in ATC and found it to improve patients' outcome within multimodality approach (Nilsson et al. 1998). Debulking as palliative surgery in ATC IVC is, however, generally not recommended, as there is no sufficient evidence for a patient's benefit within the multimodality approach, where urgently necessary systemic treatment is of highest priority(Bible et al. 2021; Haddad et al. 2018; Filetti et al. 2019; Sugitani et al. 2018). In our analyses debulking surgery was an independent predictor for a higher overall and disease-specific mortality in ATC IVC patients. This may be caused by the unfavorable constellation of peri-operative morbidity and insufficient response towards RT or systemic therapies in terms of local control. Moreover, debulking surgery is only performed in cases, where R0/R1 resection is not achievable in locally aggressive advanced disease, which is a prognostically unfavorable constellation by itself. In addition, debulking surgery postpones the start of RT and/or systemic therapy and can lead to intervention-related complications with a negative impact on the outcome.

In general, there are several specific complications after an oncologic thyroid surgery: permanent and transient uni- or bilateral recurrent laryngeal nerve palsy, injuries to the

superior laryngeal nerve, tracheomalacia, hypoparathyroidism, and fistulae (Rosato et al. 2004; Oertli and Udelsman 2007). The incidence of nerve injury, the most common specific complication, has been sufficiently decreased by the utilization of an intraoperative neurological monitoring, as suggested by some authors (Bai and Chen 2018; Zheng et al. 2013). Other complications can effectively be managed with either conservative or additional invasive approaches (Orloff et al. 2018; Campisi et al. 2013; Lee et al. 2016a; Spitzweg et al. 2017). These potential risks in the course of surgery, especially debulking, seem to outweigh the profit from this intervention because of the heterogeneous volume of the remaining tumor burden. Thus, limited (not ultra-radical) thyroidectomy, but not debulking, may be offered in selected patients with ATC IVC, since there is a promising evidence of potential profit, whereas complications can appropriately be avoided or managed. Furthermore, data suggest that at least < R2 resection has to be achieved to facilitate further therapeutic response.

In ATC, surgery is recommended to be followed by adjuvant therapy, consisting of local RT with or without simultaneous or sequential ChT, to reduce the risk of local recurrence and thus improve overall survival. The recommended radiation doses range between 20 and 75 Gy, depending on the therapeutic goal (Filetti et al. 2019; Pezzi et al. 2017). For palliative radiation, doses between 20 and 30 Gy are usually administered; for a curative therapeutic goal, doses of ≥ 40 Gy are used (Liu et al. 2016; Sugitani et al. 2018; Sun et al. 2015; Wendler et al. 2016). However, there is still disagreement about the level of doses administered to patients with a curative therapy goal. In addition to studies recommending ≥ 40 Gy for ATC patients, however, many indicate effective irradiation only at doses of ≥ 60 Gy. According to a study by Fan et al. for example, irradiation doses of ≥ 60 Gy improve overall survival ($p = 0.004$), as well as local control ($p < 0.001$) and additionally prolong median overall survival (10.6 months vs. 3.6 months)(Fan et al. 2020). Similar results were obtained in the study by Glaser et al. which indicates an effective radiation dose for a favorable outcome at ≥ 59.4 Gy (Glaser et al. 2016). A more aggressive therapy regimen with higher radiation doses not only shows a benefit in stage IVA, but also in selected patients in inoperable stage IVB or stage IVC. Higher doses have a positive effect on local control and reduce the risk of local recurrence and thus improve overall survival rates (Pezzi et al. 2017). The evaluations of Fan et al. also suggest that higher radiation doses do not necessarily mean higher toxicity and that grade 4 toxicities did not occur more frequently than with lower radiation doses (Fan et al. 2020). In our pooled analysis from the systematic review, sufficient radiation doses beyond 30 Gy correlated uni- and multivariately with a beneficial OS (Table 3, Fig. 2C). Analyses obtained from the SEER database also show RT to be an independent predictor for a beneficial OS and DSS (Suppl. Figures 1C, 2B); however, exact dosage remains unknown due to limited SEER data. Furthermore, our previous study showed that RT in advanced ATC may also offer a durable local control and can be considered safe for patients (Augustin et al. 2021).

The application of ChT, usually in combination with adjuvant RT, is still controversial. Systemic therapy is the main treatment regimen for metastatic patients, but has only a low response rate and usually leads to significant side effects with a corresponding loss of quality of life (Filetti et al. 2019). There are studies that show that ChT in ATC does not bring a survival benefit and only increases therapy-associated toxicities (Huang et al. 2019; Sun et al. 2015; Corrigan et al. 2019). Other studies, however, found a survival benefit that can be achieved by simultaneously or sequentially administered ChT (Wendler et al. 2016; Käsmann et al. 2016). Recommended ChT regimens include either single-agent therapy with paclitaxel or doxorubicin, or a combination of agents, such as carboplatin/paclitaxel and docetaxel/doxorubicin (Haddad et al. 2018; Filetti et al. 2019; Ain KB et al. (CATCHIT) Group* 2000; ; ; Sosa et al. 2014; Shimaoka et al. 1985). In our analysis, administration of ChT corresponded with beneficial OS and DSS rates in univariate analysis and also in multivariate analysis in both SEER cohorts (Suppl. Figures 1B, C, 3C, F, 4F; Fig. 4C; 5F; Tables 5 and 6), but also univariately in the pooled cohort (Fig. 2B).

Combination of all three therapeutic approaches in the course of a multimodality therapy approach shows an advantage in the vast majority of patients with regard to overall survival and progression-free survival(Haymart et al. 2013; Pezzi et al. 2017; Fan et al. 2020; Corrigan et al. 2019; Rao et al. 2017). In stage IVA and resectable stage IVB, this approach is already an established standard of care (Haddad et al. 2018; Filetti et al. 2019; Smallridge et al. 2012; Sun et al. 2015). However, some studies are extending multimodal therapy to patients in stage IVB and stage IVC. Tian et al. showed CRT in ATC patients with metastatic disease to correlate with a longer 1-year OS (HR 0.65, $p < 0.001$) (Tian et al. 2020). Depending on the physical condition of the patients and their personal expectations, a more intensive therapy regime should, therefore, be considered. The decision on the individual therapy approach should be made within the framework of an interdisciplinary expert team of oncologists, radiotherapists, endocrinologists, pathologists and surgeons. In our analyses, multimodal therapy in ATC IVC was associated with a prolonged OS and DSS in all of our cohorts on the univariate analysis (*p* value: < 0.001–0.014, Figs. 2–5, Suppl. Figures 1–4). On the multivariate analysis, it, however, did not reach any significance (Fig. 5G, Suppl. Figure 4G).

In the course of our investigation, we also evaluated the impact of older age ≥ 65 years in metastatic ATC on the OS and DSS. We found it to be an independent predictor for a higher overall mortality in both SEER databases, but not for the disease-specific mortality (Table 5, Suppl. Figures 1F, 2E, 3E, 4I; Fig. 4E). This is in line with the findings of other authors that stated age ≥ 65 and ≥ 70 years, respectively, to be an independent predictor for a shortened OS (Glaser et al. 2016; Sugitani et al. 2012; Pezzi et al. 2017). Such a difference is most likely caused by the lower performance score and lower susceptibility for intensive treatment regimens in older patients.

In addition, some authors reported a significant increase in survival of ATC patients within the last two decades due to a significantly improved patient-management (Maniakas et al. 2020). Prasongsook et al. have also shown a difference between treatment outcome in ATC patients, yet not for the multimodal approach in the metastasized ATC (Prasongsook et al. 2017). In none of our analysis, however, we were able to find any difference in the patient outcome depending on the year of their diagnosis. Conversely, we have only investigated an advanced stage ATC. These findings, however, were generated from the data of an era prior to Food and Drug Administration approvals (FDA, USA) of any of the available TKIs or immunotherapies for ATC. A combination of dabrafenib and trametinib has been approved by FDA for an advanced, *BRAF V600E/MEK* positive ATC, as it showed acceptable toxicity with an overall response rate (ORR) of 69% in May 2018 (Subbiah et al. 2018; Highlights of prescribing information xxxx). Furthermore, first results of the phase-II ATLEP trial on the combination of Lenvatinib and pembrolizumab in the metastasized ATC/PDTC showed a promising outcome with acceptable toxicity(Dierks et al. 2021). In total, not only may these therapies provide an improved survival, distant and local control rates, but it may also facilitate a reevaluation of the role of surgery in ATC stage IVC, especially when used in a neo-adjuvant setting.

Our study has several limitations, such as the retrospective nature and, hence, the risk of including hidden selection biases. In addition, SEER data on ChT and RT have been reported to have limitations in terms of sensitivity, biases and variables within the treatment sequence (Noone et al. 2016). The SEER data have, however, still a significant positive-predictive value, but have to be used with caution. In our analysis, we partially investigated patients with any tumor-directed treatment and did not evaluate any treatment-related sequences, to minimize possible biases between treated and untreated patients.

In conclusion, we were able to show that surgery to the primary tumor—thyroidectomy in any form, but not debulking—was an important factor bearing an OS and a DSS benefit for ATC patients with distant metastases from SEER database. Furthermore, sufficient RT (≥ 30 Gy), administration of ChT or combined multimodal treatment and young age < 65 years had a significant influence on the OS and DSS from both pooled and SEER-based analysis.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00432-022-04223-7.

Author contributions Conceptualization, methodology, formal analysis, investigation, data curation and writing the manuscript: LK and DO; supervision, CB and JR; project administration, LK and CS. All authors have read and agreed to the published version of the manuscript

Funding Open Access funding enabled and organized by Projekt DEAL. The authors have not disclosed any funding.

Declarations

Conflict of interest The authors declare no conflict of interest.

Open Access This article is licensed under a Creative Commons Attribution 4.0 International License, which permits use, sharing, adaptation, distribution and reproduction in any medium or format, as long as you give appropriate credit to the original author(s) and the source, provide a link to the Creative Commons licence, and indicate if changes were made. The images or other third party material in this article are included in the article's Creative Commons licence, unless indicated otherwise in a credit line to the material. If material is not included in the article's Creative Commons licence and your intended use is not permitted by statutory regulation or exceeds the permitted use, you will need to obtain permission directly from the copyright holder. To view a copy of this licence, visit http://creativecommons.org/licenses/by/4.0/.

References

Ain KB, Egorin MJ, DeSimone PA, Collaborative Anaplastic Thyroid Cancer Health Intervention Trials (CATCHIT) Group (2000) Treatment of anaplastic thyroid carcinoma with paclitaxel: phase 2 trial using ninety-six-hour infusion. Thyroid 10:587–594. https://doi.org/10.1089/thy.2000.10.587

Akaishi J, Sugino K, Kitagawa W, Nagahama M, Kameyama K, Shimizu K, Ito K, Ito K (2011) Prognostic factors and treatment outcomes of 100 cases of anaplastic thyroid carcinoma. Thyroid 21:1183–1189. https://doi.org/10.1089/thy.2010.0332

Aslan ZAT, Granados-García M, Luna-Ortiz K, Guerrero-Huerta FJ, Gómez-Pedraza A, Ñamendys-Silva SA, Meneses-García A, Ordoñez-Mosquera JM (2014) Anaplastic thyroid cancer: multimodal treatment results. 13

Augustin T, Oliinyk D, Rauch J, Koehler VF, Spitzweg C, Belka C, Käsmann L (2021) Radiation to the primary tumor in metastatic anaplastic thyroid cancer. In Vivo 35:461–465. https://doi.org/10.21873/invivo.12279

Baek S-K, Lee M-C, Hah JH, Ahn S-H, Son Y-I, Rho Y-S, Chung P-S, Lee Y-S, Koo BS, Jung K-Y, Lee B-J (2017) Role of surgery in the management of anaplastic thyroid carcinoma: Korean nationwide multicenter study of 329 patients with anaplastic thyroid carcinoma, 2000 to 2012: surgical role in anaplastic thyroid carcinoma. Head Neck 39:133–139. https://doi.org/10.1002/hed.24559

Bai B, Chen W (2018) Protective effects of intraoperative nerve monitoring (IONM) for recurrent laryngeal nerve injury in thyroidectomy: meta-analysis. Sci Rep 8:7761. https://doi.org/10.1038/s41598-018-26219-5

Bhatia A, Rao A, Ang K-K, Garden AS, Morrison WH, Rosenthal DI, Evans DB, Clayman G, Sherman SI, Schwartz DL (2009) Anaplastic thyroid cancer: clinical outcomes with conformal radiotherapy. Head Neck NA-NA. https://doi.org/10.1002/hed.21257

Bible KC, Kebebew E, Brierley J, Brito JP, Cabanillas ME, Clark TJ, Di Cristofano A, Foote R, Giordano T, Kasperbauer J, Newbold K, Nikiforov YE, Randolph G, Rosenthal MS, Sawka AM, Shah M, Shaha A, Smallridge R, Wong-Clark CK (2021) 2021 American thyroid association guidelines for management of patients with anaplastic thyroid cancer: American thyroid association anaplastic thyroid cancer guidelines task force. Thyroid 31:337–386. https://doi.org/10.1089/thy.2020.0944

Brignardello E, Gallo M, Baldi I, Palestini N, Piovesan A, Grossi E, Ciccone G, Boccuzzi G (2007) Anaplastic thyroid carcinoma: clinical outcome of 30 consecutive patients referred to a single institution in the past 5 years. Eur J Endocrinol 156:425–430. https://doi.org/10.1530/EJE-06-0677

Brignardello E, Palestini N, Felicetti F, Castiglione A, Piovesan A, Gallo M, Freddi M, Ricardi U, Gasparri G, Ciccone G, Arvat E, Boccuzzi G (2014) Early surgery and survival of patients with anaplastic thyroid carcinoma: analysis of a case series referred to a single institution between 1999 and 2012. Thyroid 24:1600–1606. https://doi.org/10.1089/thy.2014.0004

Busnardo B, Daniele O, Pelizzo MR, Mazzarotto R, Nacamulli D, DeVido D, Mian C, Girelli ME (2000) A multimodality therapeutic approach in anaplastic thyroid carcinoma: study on 39 patients. J Endocrinol Invest 23:755–761. https://doi.org/10.1007/BF03345066

Campisi CC, Boccardo F, Piazza C, Campisi C (2013) Evolution of chylous fistula management after neck dissection. Curr Opin Otolaryngol Head Neck Surg 21:150–156. https://doi.org/10.1097/MOO.0b013e32835e9d97

Corrigan KL, Williamson H, Elliott Range D, Niedzwiecki D, Brizel DM, Mowery YM (2019) Treatment outcomes in anaplastic thyroid cancer. J Thyroid Res 2019:1–11. https://doi.org/10.1155/2019/8218949

Dal Maso L, Tavilla A, Pacini F, Serraino D, van Dijk BAC, Chirlaque MD, Capocaccia R, Larrañaga N, Colonna M, Agius D, Ardanaz E, Rubió-Casadevall J, Kowalska A, Virdone S, Mallone S, Amash H, De Angelis R, Hackl M, Zielonke N, Van Eycken E, Henau K, Valerianova Z, Dimitrova N, Sekerija M, Dušek L, Zvolský M, Storm H, Engholm G, Mägi M, Aareleid T, Malila N, Seppä K, Velten M, Guizard AV, Faivre J, Woronoff AS, Tretarre B, Bossard N, Uhry Z, Colonna M, Molinié F, Bara S, Schvartz C, Lapôtre-Ledoux B, Grosclaude P, Stabenow R, Luttmann S, Eberle A, Brenner H, Nennecke A, Engel J, Schubert-Fritschle G, Heidrich J, Holleczek B, Katalinic A, Jónasson JG, Tryggvadóttir L, Comber H, Mazzoleni G, Bulatko A, Buzzoni C, Giacomin A, Sutera Sardo A, Mazzei A, Ferretti S, Barchielli A, Caldarella A, Gatta G, Sant M, Amash H, Amati C, Baili P, Berrino F, Bonfarnuzzo S, Botta L, Capocaccia R, Di Salvo F, Foschi R, Margutti C, Meneghini E, Minicozzi P, Trama A, Serraino D, Zucchetto A, De Angelis R, Caldora M, Carrani E, Francisci S, Mallone S, Pierannunzio D, Roazzi P, Rossi S, Santaquilani M, Tavilla A, Pannozzo F, Busco S, Filiberti RA, Vercelli M, Ricci P, Autelitano M, Spagnoli G, Cirilli C, Fusco M, Vitale MF, Usala M, Vitale F, Ravazzolo B, Michiara M, Tumino R, Mangone L, Vicentini M, Falcini F, Iannelli A, Sechi O, Cesaraccio R, Piffer S, Madeddu A, Tisano F, Maspero S, Fanetti AC, Zanetti R, Rosso S, Candela P, Scuderi T, Stracci F, Rocca A, Tagliabue G, Contiero P, Rugge M, Tognazzo S, Pildava S, Smailyte G, Calleja N, Agius D, Johannesen TB, Rachtan J, Góźdź S, Mężyk R, Błaszczyk J, Bębenek M, Bielska-Lasota M, Forjaz de Lacerda G, Bento MJ, Castro C, Miranda A, Mayer-da-Silva A, Safaei Diba C, Primic-Zakelj M, Errezola M, Bidaurrazaga J, Díaz García JM, Marcos-Navarro AI, Marcos-Gragera R, Izquierdo Font A, Sanchez MJ, Molina E, Navarro C, Chirlaque MD, Moreno-Iribas C, Ardanaz E, Galceran J, Carulla M, Lambe M, Khan S, Mousavi M, Bouchardy C, Usel M, Ess SM, Frick H, Lorez M, Ess SM, Herrmann C, Bordoni A, Spitale A, Konzelmann I, Visser O, Ho V, Otter R, Coleman M, Allemani C, Rachet B, Rashbass J, Broggio J, Verne J, Gavin A, Donnelly C, Brewster DH, Huws DW, White C (2017) Survival of 86,690 patients with thyroid cancer: a population-based study in 29 European countries from EUROCARE-5. Eur J Cancer 77:140–152. https://doi.org/10.1016/j.ejca.2017.02.023

De Crevoisier R, Baudin E, Bachelot A, Leboulleux S, Travagli J-P, Caillou B, Schlumberger M (2004) Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy. Int J Radiat Oncol 60:1137–1143. https://doi.org/10.1016/j.ijrobp.2004.05.032

de Ridder M, Nieveen van Dijkum E, Engelsman A, Kapiteijn E, Klümpen H-J, Rasch CRN (2020) Anaplastic thyroid carcinoma: a nationwide cohort study on incidence, treatment and survival in the Netherlands over 3 decades. Eur J Endocrinol 183:203–209. https://doi.org/10.1530/EJE-20-0080

Derbel O, Limem S, Ségura-Ferlay C, Lifante J-C, Carrie C, Peix J-L, Borson-Chazot F, Bournaud C, Droz J-P, de la Fouchardière C (2011) Results of combined treatment of anaplastic thyroid carcinoma (ATC). BMC Cancer 11:469. https://doi.org/10.1186/1471-2407-11-469

Dierks C, Seufert J, Aumann K, Ruf J, Klein C, Kiefer S, Rassner M, Boerries M, Zielke A, la Rosee P, Meyer PT, Kroiss M, Weißenberger C, Schumacher T, Metzger P, Weiss H, Smaxwil C, Laubner K, Duyster J, von Bubnoff N, Miething C, Thomusch O (2021) Combination of lenvatinib and pembrolizumab is an effective treatment option for anaplastic and poorly differentiated thyroid carcinoma. Thyroid 31:1076–1085. https://doi.org/10.1089/thy.2020.0322

Dumke A-K, Pelz T, Vordermark D (2014) Long-term results of radiotherapy in anaplastic thyroid cancer. Radiat Oncol 9:90. https://doi.org/10.1186/1748-717X-9-90

Fan D, Ma J, Bell AC, Groen AH, Olsen KS, Lok BH, Leeman JE, Anderson E, Riaz N, McBride S, Ganly I, Shaha AR, Sherman EJ, Tsai CJ, Kang JJ, Lee NY (2020) Outcomes of multimodal therapy in a large series of patients with anaplastic thyroid cancer. Cancer 126:444–452. https://doi.org/10.1002/cncr.32548

Filetti S, Durante C, Hartl D, Leboulleux S, Locati LD, Newbold K, Papotti MG, Berruti A (2019) Thyroid cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-up. Ann Oncol 30:1856–1883. https://doi.org/10.1093/annonc/mdz400

Glaser SM, Mandish SF, Gill BS, Balasubramani GK, Clump DA, Beriwal S (2016) Anaplastic thyroid cancer: prognostic factors, patterns of care, and overall survival: anaplastic thyroid cancer. Head Neck 38:E2083–E2090. https://doi.org/10.1002/hed.24384

Goffredo P, Thomas SM, Adam MA, Sosa JA, Roman SA (2015) Impact of timeliness of resection and thyroidectomy margin status on survival for patients with anaplastic thyroid cancer: an analysis of 335 cases. Ann Surg Oncol 22:4166–4174. https://doi.org/10.1245/s10434-015-4742-6

Gui W, Zhu W, Lu W, Shang C, Zheng F, Lin X, Li H (2020) Development and validation of a prognostic nomogram to predict overall survival and cancer-specific survival for patients with anaplastic thyroid carcinoma. PeerJ 8:e9173. https://doi.org/10.7717/peerj.9173

Haddad RI, Nasr C, Bischoff L, Busaidy NL, Byrd D, Callender G, Dickson P, Duh Q-Y, Ehya H, Goldner W, Haymart M, Hoh C, Hunt JP, Iagaru A, Kandeel F, Kopp P, Lamonica DM, McIver B, Raeburn CD, Ridge JA, Ringel MD, Scheri RP, Shah JP, Sippel R, Smallridge RC, Sturgeon C, Wang TN, Wirth LJ, Wong RJ, Johnson-Chilla A, Hoffmann KG, Gurski LA (2018) NCCN guidelines insights: thyroid carcinoma, version 2.2018. J Natl Compr Canc Netw 16:1429–1440. https://doi.org/10.6004/jnccn.2018.0089

Haigh PI, Ituarte PHG, Wu HS, Treseler PA, Posner MD, Quivey JM, Duh QY, Clark OH (2001) Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. Cancer 31:2335–2342

Haigh PI, Ituarte PHG, Wu HS, Treseler PA, Posner MD, Quivey JM, Duh QY, Clark OH (2001) Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival. Cancer 91:2335–2342. https://doi.org/10.1002/1097-0142(20010615)91:12%3c2335::AID-CNCR1266%3e3.0.CO;2-1

Haymart MR, Banerjee M, Yin H, Worden F, Griggs JJ (2013) Marginal treatment benefit in anaplastic thyroid cancer: treatment of anaplastic thyroid cancer. Cancer 119:3133–3139. https://doi.org/10.1002/cncr.28187

Highlights of prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/202806s010lbl.pdf

Huang N, Shi X, Lei B, Wei W, Lu Z, Yu P, Wang Y, Ji Q, Wang Y (2019) An update of the appropriate treatment strategies in anaplastic thyroid cancer: a population-based study of 735 patients. Int J Endocrinol 2019:1–7. https://doi.org/10.1155/2019/8428547

Ito K, Hanamura T, Murayama K, Okada T, Watanabe T, Harada M, Ito T, Koyama H, Kanai T, Maeno K, Mochizuki Y, Amano J (2012) Multimodality therapeutic outcomes In anaplastic thyroid carcinoma: improved survival in subgroups of patients with localized primary tumors. Head Neck 34:230–237. https://doi.org/10.1002/hed.21721

Jacobsen A-B, Grøholt KK, Lorntzsen B, Osnes TA, Falk RS, Sigstad E (2017) Anaplastic thyroid cancer and hyperfractionated accelerated radiotherapy (HART) with and without surgery. Eur Arch Otorhinolaryngol 274:4203–4209. https://doi.org/10.1007/s00405-017-4764-8

Käsmann L, Janssen S, Rades D (2016) Karnofsky performance score, radiation dose and nodal status predict survival of elderly patients irradiated for limited-disease small-cell lung cancer. Anticancer Res 36:4177–4180

Kebebew E, Greenspan FS, Clark OH, Woeber KA, McMillan A (2005) Anaplastic thyroid carcinoma: treatment outcome and prognostic factors. Cancer 103:1330–1335. https://doi.org/10.1002/cncr.20936

Kihara M, Miyauchi A, Yamauchi A, Yokomise H (2004) Prognostic factors of anaplastic thyroid carcinoma. Surg Today 34:394–398. https://doi.org/10.1007/s00595-003-2737-6

Kim TY, Kim KW, Jung TS, Kim JM, Kim SW, Chung K-W, Kim EY, Gong G, Oh YL, Cho SY, Yi KH, Kim WB, Park DJ, Chung JH, Cho BY, Shong YK (2007) Prognostic factors for Korean patients with anaplastic thyroid carcinoma. Head Neck 29:765–772. https://doi.org/10.1002/hed.20578

Kitamura Y, Shimizu K, Nagahama M, Sugino K, Ozaki O, Mimura T, Ito K, Ito K, Tanaka S (1999) Immediate causes of death in thyroid carcinoma: clinicopathological analysis of 161 fatal cases. J Clin Endocrinol Metabol 84:4043–4049

Lee DY, Won J-K, Lee S-H, Park DJ, Jung KC, Sung M-W, Wu H-G, Kim KH, Park YJ, Hah JH (2016a) Changes of clinicopathologic characteristics and survival outcomes of anaplastic and poorly differentiated thyroid carcinoma. Thyroid 26:404–413. https://doi.org/10.1089/thy.2015.0316

Lee DY, Won J-K, Choi HS, Park DJ, Jung KC, Sung M-W, Kim KH, Hah JH, Park YJ (2016b) recurrence and survival after gross total removal of resectable undifferentiated or poorly differentiated thyroid carcinoma. Thyroid 26:1259–1268. https://doi.org/10.1089/thy.2016.0147

Lim SM, Shin S-J, Chung WY, Park CS, Nam K-H, Kang S-W, Keum KC, Kim JH, Cho JY, Hong YK, Cho BC (2012) Treatment outcome of patients with anaplastic thyroid cancer: a single center experience. Yonsei Med J 53:352. https://doi.org/10.3349/ymj.2012.53.2.352

Liu T-R, Xiao Z-W, Xu H-N, Long Z, Wei F-Q, Zhuang S-M, Sun X-M, Xie L-E, Mu J-S, Yang A-K, Zhang G-P, Fan Y (2016) Treatment and prognosis of anaplastic thyroid carcinoma: a clinical study of 50 cases. PLoS ONE 11:e0164840. https://doi.org/10.1371/journal.pone.0164840

Maniakas A, Dadu R, Busaidy NL, Wang JR, Ferrarotto R, Lu C, Williams MD, Gunn GB, Hofmann M-C, Cote G, Sperling J, Gross ND, Sturgis EM, Goepfert RP, Lai SY, Cabanillas ME, Zafereo M (2020) Evaluation of overall survival in patients with anaplastic thyroid carcinoma, 2000–2019. JAMA Oncol 6:1397. https://doi.org/10.1001/jamaoncol.2020.3362

McIver B, Hay ID, Giuffrida DF, Dvorak CE, Grant CS, Thompson GB, van Heerden JA, Goellner JR (2001) Anaplastic thyroid carcinoma: a 50-year experience at a single institution. Surgery 130:1028–1034. https://doi.org/10.1067/msy.2001.118266

Mohebati A, DiLorenzo M, Palmer F, Patel SG, Pfister D, Lee N, Tuttle RM, Shaha AR, Shah JP, Ganly I (2014) Anaplastic thyroid carcinoma: a 25-year single-institution experience. Ann Surg Oncol 21:1665–1670. https://doi.org/10.1245/s10434-014-3545-5

Neff RL, Farrar WB, Kloos RT, Burman KD (2008) Anaplastic thyroid cancer. Endocrinol Metab Clin North Am 37:525–538. https://doi.org/10.1016/j.ecl.2008.02.003

Nilsson O, Lindeberg J, Zedenius J, Ekman E, Tennvall J, Blomgren H, Grimelius L, Lundell G, Wallin G (1998) Anaplastic giant cell carcinoma of the thyroid gland: treatment and survival over a 25-year period. World J Surg 22:725–730. https://doi.org/10.1007/s002689900460

Noone A-M, Lund JL, Mariotto A, Cronin K, McNeel T, Deapen D, Warren JL (2016) Comparison of SEER treatment data with medicare claims. Med Care 54:e55–e64. https://doi.org/10.1097/MLR.0000000000000073

Oertli D, Udelsman R (2007) Surgery of the thyroid and parathyroid glands. Springer, Berlin, New York

Orloff LA, Wiseman SM, Bernet VJ, Fahey TJ, Shaha AR, Shindo ML, Snyder SK, Stack BC, Sunwoo JB, Wang MB, For the American Thyroid Association Surgical Affairs Committee Writing Task Force (2018) American thyroid association statement on postoperative hypoparathyroidism: diagnosis, prevention, and management in adults. Thyroid 28:830–841. https://doi.org/10.1089/thy.2017.0309

Passler C, Scheuba C, Prager G, Kaserer K, Flores JA, Vierhapper H, Niederle B (1999) Anaplastic (undifferentiated) thyroid carcinoma (ATC). Langenbecks Arch Surg 384:284–293. https://doi.org/10.1007/s004230050205

Paunovic IR, Sipetic SB, Zoric GV, Diklic AD, Savic DV, Marinkovic J, Zivaljevic VR (2015) Survival and prognostic factors of anaplastic thyroid carcinoma. Acta Chir Belg 115:62–67. https://doi.org/10.1080/00015458.2015.11681068

Pezzi TA, Mohamed ASR, Sheu T, Blanchard P, Sandulache VC, Lai SY, Cabanillas ME, Williams MD, Pezzi CM, Lu C, Garden AS, Morrison WH, Rosenthal DI, Fuller CD, Gunn GB (2017) Radiation therapy dose is associated with improved survival for unresected anaplastic thyroid carcinoma: outcomes from the national cancer data base: unresected anaplastic thyroid carcinoma. Cancer 123:1653–1661. https://doi.org/10.1002/cncr.30493

Pierie J-PEN, Muzikansky A, Gaz RD, Faquin WC, Ott MJ (2002) The effect of surgery and radiotherapy on outcome of anaplastic thyroid carcinoma. Ann Surg Oncol 9:57–64. https://doi.org/10.1245/aso.2002.9.1.57

Prasongsook N, Kumar A, Chintakuntlawar AV, Foote RL, Kasperbauer J, Molina J, Garces Y, Ma D, Wittich MAN, Rubin J, Richardson R, Morris J, Hay I, Fatourechi V, McIver B, Ryder M, Thompson G, Grant C, Richards M, Sebo TJ, Rivera M, Suman V, Jenkins SM, Smallridge RC, Bible KC (2017) Survival in response to multimodal therapy in anaplastic thyroid cancer. J

Clin Endocrinol Metab 102:4506–4514. https://doi.org/10.1210/jc.2017-01180

Rao SN, Zafereo M, Dadu R, Busaidy NL, Hess K, Cote GJ, Williams MD, William WN, Sandulache V, Gross N, Gunn GB, Lu C, Ferrarotto R, Lai SY, Cabanillas ME (2017) Patterns of treatment failure in anaplastic thyroid carcinoma. Thyroid 27:672–681. https://doi.org/10.1089/thy.2016.0395

Roche B, Larroumets G, Dejax C, Kwiatkowsi F, Desbiez F, Thieblot P, Tauveron I (2010) Epidemiology, clinical presentation, treatment and prognosis of a regional series of 26 anaplastic thyroid carcinomas (ATC) Comparison with the Literature. Ann Endocrinol 71:38–45. https://doi.org/10.1016/j.ando.2009.10.013

Rosato L, Avenia N, Bernante P, De Palma M, Gulino G, Nasi PG, Pelizzo MR, Pezzullo L (2004) Complications of thyroid surgery: analysis of a multicentric study on 14,934 patients operated on in Italy over 5 years. World J Surg 28:271–276. https://doi.org/10.1007/s00268-003-6903-1

Shimaoka K, Schoenfeld DA, Dewys WD, Creech RH, Deconti R (1985) A randomized trial of doxorubicin versus doxorubicin plus cisplatin in patients with advanced thyroid carcinoma. Cancer 56:2155–2160. https://doi.org/10.1002/1097-0142(19851101)56:9%3c2155::AID-CNCR2820560903%3e3.0.CO;2-E

Smallridge RC, Ain KB, Asa SL, Bible KC, Brierley JD, Burman KD, Kebebew E, Lee NY, Nikiforov YE, Rosenthal MS, Shah MH, Shaha AR, Tuttle for the American Thyroid Ass RM (2012) American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer. Thyroid 22:1104–1139. https://doi.org/10.1089/thy.2012.03022

So K, Smith RE, Davis SR (2017) Radiotherapy in anaplastic thyroid carcinoma: an Australian experience. J Med Imaging Radiat Oncol 61:279–287. https://doi.org/10.1111/1754-9485.12552

Sosa JA, Elisei R, Jarzab B, Balkissoon J, Lu S, Bal C, Marur S, Gramza A, Yosef RB, Gitlitz B, Haugen BR, Ondrey F, Lu C, Karandikar SM, Khuri F, Licitra L, Remick SC (2014) Randomized safety and efficacy study of fosbretabulin with paclitaxel/carboplatin against anaplastic thyroid carcinoma. Thyroid 24:232–240. https://doi.org/10.1089/thy.2013.0078

Spitzweg C, Reincke M, Gärtner R (2017) Schilddrüsennotfälle: thyreotoxische krise und myxödemkoma. Internist 58:1011–1019. https://doi.org/10.1007/s00108-017-0306-0

Stavas MJ, Shinohara ET, Attia A, Ning MS, Friedman JM, Cmelak AJ (2014) Short course high dose radiotherapy in the treatment of anaplastic thyroid carcinoma. J Thyroid Res 2014:1–7. https://doi.org/10.1155/2014/764281

Subbiah V, Kreitman RJ, Wainberg ZA, Cho JY, Schellens JHM, Soria JC, Wen PY, Zielinski C, Cabanillas ME, Urbanowitz G, Mookerjee B, Wang D, Rangwala F, Keam B (2018) Dabrafenib and trametinib treatment in patients with locally advanced or metastatic *BRAF* v600–mutant anaplastic thyroid cancer. J Clin Oncol 36:7–13. https://doi.org/10.1200/JCO.2017.73.6785

Sugitani I, Miyauchi A, Sugino K, Okamoto T, Yoshida A, Suzuki S (2012) Prognostic factors and treatment outcomes for anaplastic thyroid carcinoma: ATC research consortium of japan cohort study of 677 patients. World J Surg 36:1247–1254. https://doi.org/10.1007/s00268-012-1437-z

Sugitani I, Hasegawa Y, Sugasawa M, Tori M, Higashiyama T, Miyazaki M, Hosoi H, Orita Y, Kitano H (2014) Super-radical surgery for anaplastic thyroid carcinoma: a large cohort study using the anaplastic thyroid carcinoma research consortium of Japan database: Super-radical surgery for anaplastic thyroid carcinoma. Head Neck 36:328–333. https://doi.org/10.1002/hed.23295

Sugitani I, Onoda N, Ito K, Suzuki S (2018) Management of anaplastic thyroid carcinoma: the fruits from the ATC research consortium of Japan. J Nippon Med Sch 85:18–27. https://doi.org/10.1272/jnms.2018_85-3

Sun C, Li C, Hu Z, Li X, He J, Song M, Li G, Zhang F, Li Q (2015) Influence of risk grouping on therapeutic decisions in patients with anaplastic thyroid carcinoma. Eur Arch Otorhinolaryngol 272:985–993. https://doi.org/10.1007/s00405-014-2937-2

Takahashi N, Matsushita H, Umezawa R, Yamamoto T, Ishikawa Y, Katagiri Y, Tasaka S, Takeda K, Fukui K, Kadoya N, Ito K, Jingu K (2019) Hypofractionated radiotherapy for anaplastic thyroid carcinoma: 15 years of experience in a single institution. Eur Thyroid J 8:24–30. https://doi.org/10.1159/000493315

Tennvall J, Lundell G, Wahlberg P, Bergenfelz A, Grimelius L, Åkerman M, Hjelm Skog A-L, Wallin G (2002) Anaplastic thyroid carcinoma: three protocols combining doxorubicin, hyperfractionated radiotherapy and surgery. Br J Cancer 86:1848–1853. https://doi.org/10.1038/sj.bjc.6600361

Tian S, Switchenko JM, Fei T, Press RH, Abugideiri M, Saba NF, Owonikoko TK, Chen AY, Beitler JJ, Curran WJ, Gillespie TW, Higgins KA (2020) Survival advantage of chemoradiotherapy in anaplastic thyroid carcinoma: propensity score matched analysis with multiple subgroups. Head Neck 42:678–687. https://doi.org/10.1002/hed.26042

Troch M, Koperek O, Scheuba C, Dieckmann K, Hoffmann M, Niederle B, Raderer M (2010) High efficacy of concomitant treatment of undifferentiated (anaplastic) thyroid cancer with radiation and docetaxel. J Clin Endocrinol Metab 95:E54–E57. https://doi.org/10.1210/jc.2009-2827

Venkatesh YSS, Ordonez NG, Schultz PN, Hickey RC, Goepfert H, Samaan NA (1990) Anaplastic carcinoma of the thyroid: A clinicopathologic study of 121 cases. Cancer 66:321–330. https://doi.org/10.1002/1097-0142(19900715)66:2%3c321::AID-CNCR2820660221%3e3.0.CO;2-A

Wendler J, Kroiss M, Gast K, Kreissl MC, Allelein S, Lichtenauer U, Blaser R, Spitzweg C, Fassnacht M, Schott M, Führer D, Tiedje V (2016) Clinical presentation, treatment and outcome of anaplastic thyroid carcinoma: results of a multicenter study in Germany. Eur J Endocrinol 175:521–529. https://doi.org/10.1530/EJE-16-0574

Yau T, Lo CY, Epstein RJ, Lam AKY, Wan KY, Lang BH (2008) Treatment outcomes in anaplastic thyroid carcinoma: survival improvement in young patients with localized disease treated by combination of surgery and radiotherapy. Ann Surg Oncol 15:2500–2505. https://doi.org/10.1245/s10434-008-0005-0

Zheng S, Xu Z, Wei Y, Zeng M, He J (2013) Effect of intraoperative neuromonitoring on recurrent laryngeal nerve palsy rates after thyroid surgery—A meta-analysis. J Formos Med Assoc 112:463–472. https://doi.org/10.1016/j.jfma.2012.03.003

Zivaljevic V, Tausanovic K, Paunovic I, Diklic A, Kalezic N, Zoric G, Sabljak V, Vekic B, Zivic R, Marinkovic J, Sipetic S (2014) Age as a prognostic factor in anaplastic thyroid cancer. Int J Endocrinol 2014:1–5. https://doi.org/10.1155/2014/240513

Publisher's Note Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.

9. Literaturverzeichnis

[1] L. Davies und H. G. Welch, „Increasing incidence of thyroid cancer in the United States, 1973- 2002.“, *JAMA*, Bd. 295, Nr. 18, S. 2164–2167, Mai 2006, doi: 10.1001/jama.295.18.2164

[2] R. C. Smallridge und J. A. Copland, „Anaplastic Thyroid Carcinoma: Pathogenesis and Emerging Therapies“, *Clin. Oncol.*, Bd. 22, Nr. 6, S. 486–497, Aug. 2010, doi: 10.1016/j.clon.2010.03.013

[3] H. Sung, J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal, und F. Bray, „Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries“, *CA. Cancer J. Clin.*, Bd. 71, Nr. 3, S. 209–249, Mai 2021, doi: 10.3322/caac.21660

[4] L. Dal Maso, A. Tavilla, F. Pacini, D. Serraino, B. A. C. van Dijk, M. D. Chirlaque, R. Capocaccia, N. Larrañaga, M. Colonna, D. Agius, E. Ardanaz, J. Rubió-Casadevall, A. Kowalska, S. Virdone, S. Mallone, H. Amash, R. De Angelis, M. Hackl, N. Zielonke, E. Van Eycken, K. Henau, Z. Valerianova, N. Dimitrova, M. Sekerija, L. Dušek, M. Zvolský, H. Storm, G. Engholm, M. Mägi, T. Aareleid, N. Malila, K. Seppä, M. Velten, A. V. Guizard, J. Faivre, A. S. Woronoff, B. Tretarre, N. Bossard, Z. Uhry, M. Colonna, F. Molinié, S. Bara, C. Schvartz, B. Lapôtre-Ledoux, P. Grosclaude, R. Stabenow, S. Luttmann, A. Eberle, H. Brenner, A. Nennecke, J. Engel, G. Schubert-Fritschle, J. Heidrich, B. Holleczek, A. Katalinic, J. G. Jónasson, L. Tryggvadóttir, H. Comber, G. Mazzoleni, A. Bulatko, C. Buzzoni, A. Giacomin, A. Sutera Sardo, A. Mazzei, S. Ferretti, A. Barchielli, A. Caldarella, G. Gatta, M. Sant, H. Amash, C. Amati, P. Baili, F. Berrino, S. Bonfarnuzzo, L. Botta, R. Capocaccia, F. Di Salvo, R. Foschi, C. Margutti, E. Meneghini, P. Minicozzi, A. Trama, D. Serraino, A. Zucchetto, R. De Angelis, M. Caldora, E. Carrani, S. Francisci, S. Mallone, D. Pierannunzio, P. Roazzi, S. Rossi, M. Santaquilani, A. Tavilla, F. Pannozzo, S. Busco, R. A. Filiberti, M. Vercelli, P. Ricci, M. Autelitano, *u. a.*, „Survival of 86,690 patients with thyroid cancer: A population-based study in 29 European countries from EUROCARE-5“, *Eur. J. Cancer*, Bd. 77, S. 140–152, Mai 2017, doi: 10.1016/j.ejca.2017.02.023

[5] F. Erdmann, C. Spix, A. Katalinic, M. Christ, J. Folkerts, J. Hansmann, K. Kranzhöfer, B. Kunz, K. Manegold, A. Penzkofer, K. Treml, G. Vollmer, S. Weg-Remers, B. Barnes, N. Buttmann-Schweiger, S. Dahm, J. Fiebig, M. Franke, I. Gurung-Schönfeld, J. Haberland, M. Imhoff, K. Kraywinkel, A. Starker, P. von Berenberg-Gossler, und A. Wienecke, „Krebs in Deutschland für 2017/2018“, Nr. 13, S. 126-129, 2021. doi: http://dx.doi.org/10.25646/8353. Verfügbar unter: https://www.krebsdaten.de/Krebs/DE/Content/Publikationen/Krebs_in_Deutschland/kid_2021/kid_2021_c73_schilddruese.pdf?__blob=publicationFile. [Zugegriffen: 4. September 2022]

[6] G. Nagaiah, A. Hossain, C. J. Mooney, J. Parmentier, und S. C. Remick, „Anaplastic Thyroid Cancer: A Review of Epidemiology, Pathogenesis, and Treatment“, *J. Oncol.*, Bd. 2011, S. 1–13, 2011, doi: 10.1155/2011/542358

[7] R. L. Neff, W. B. Farrar, R. T. Kloos, und K. D. Burman, „Anaplastic Thyroid Cancer“, *Endocrinol. Metab. Clin. North Am.*, Bd. 37, Nr. 2, S. 525–538, Juni 2008, doi: 10.1016/j.ecl.2008.02.003

[8] *Lloyd, R. V., Osamura, R. Y., Kloppel, G. & Rosai, J. (eds) WHO Classification of Tumours of Endocrine Organs. 4th ed. (IARC, 2017).*

[9] A. Porter und D. J. Wong, „Perspectives on the Treatment of Advanced Thyroid Cancer: Approved Therapies, Resistance Mechanisms, and Future Directions“, *Front. Oncol.*, Bd. 10, S. 592202, Jan. 2021, doi: 10.3389/fonc.2020.592202

[10] „Sherman S. I. (2003). Thyroid carcinoma. Lancet (London, England), 361(9356), 501–511. https://doi.org/10.1016/s0140-6736(03)12488-9“.

[11] L. Davies und H. G. Welch, „Epidemiology of head and neck cancer in the United States“, *Otolaryngol. Neck Surg.*, Bd. 135, Nr. 3, S. 451–457, Sep. 2006, doi: 10.1016/j.otohns.2006.01.029

[12] A. Verdecchia, S. Francisci, H. Brenner, G. Gatta, A. Micheli, L. Mangone, und I. Kunkler,

„Recent cancer survival in Europe: a 2000–02 period analysis of EUROCARE-4 data“, *Lancet Oncol.*, Bd. 8, Nr. 9, S. 784–796, Sep. 2007, doi: 10.1016/S1470-2045(07)70246-2

[13] I. Ganly, I. J. Nixon, L. Y. Wang, F. L. Palmer, J. C. Migliacci, A. Aniss, M. Sywak, A. E. Eskander, J. L. Freeman, M. J. Campbell, W. T. Shen, F. Vaisman, D. Momesso, R. Corbo, M. Vaisman, A. Shaha, R. M. Tuttle, J. P. Shah, und S. G. Patel, „Survival from Differentiated Thyroid Cancer: What Has Age Got to Do with It?“, *Thyroid*, Bd. 25, Nr. 10, S. 1106–1114, Okt. 2015, doi: 10.1089/thy.2015.0104

[14] G. Graceffa, G. Salamone, S. Contino, F. Saputo, A. Corigliano, G. Melfa, M. P. Proclamà, P. Richiusa, S. Mazzola, R. Tutino, G. Orlando, und G. Scerrino, „Risk Factors for Anaplastic Thyroid Carcinoma: A Case Series From a Tertiary Referral Center for Thyroid Surgery and Literature Analysis“, *Front. Oncol.*, Bd. 12, S. 948033, Juli 2022, doi: 10.3389/fonc.2022.948033

[15] V. Zivaljevic, N. Slijepcevic, I. Paunovic, A. Diklic, N. Kalezic, J. Marinkovic, R. Zivic, B. Vekic, und S. Sipetic, „Risk Factors for Anaplastic Thyroid Cancer“, *Int. J. Endocrinol.*, Bd. 2014, S. 1–6, 2014, doi: 10.1155/2014/815070

[16] R. Parameswaran, S. Brooks, und G. P. Sadler, „Molecular pathogenesis of follicular cell derived thyroid cancers“, *Int. J. Surg.*, Bd. 8, Nr. 3, S. 186–193, 2010, doi: 10.1016/j.ijsu.2010.01.005

[17] Y. Nikiforov und D. R. Gnepp, „Pediatric thyroid cancer after the chernobyl disaster. Pathomorphologic study of 84 cases (1991–1992) from the republic of Belarus“, *Cancer*, Bd. 74, Nr. 2, S. 748–766, Juli 1994, doi: 10.1002/1097-0142(19940715)74:2<748::AID-CNCR2820740231>3.0.CO;2-H

[18] A. W. Furmanchuk, J. I. Averkin, B. Egloff, C. Ruchti, T. Abelin, W. Schäppi, und E. A. Korotkevich, „Pathomorphological findings in thyroid cancers of children from the Republic of Belarus: a study of 86 cases occurring between 1986 ('post-Chernobyl') and 1991“, *Histopathology*, Bd. 21, Nr. 5, S. 401–408, Nov. 1992, doi: 10.1111/j.1365-2559.1992.tb00423.x

[19] E. D. Williams, „13 The aetiology of thyroid tumours“, *Clin. Endocrinol. Metab.*, Bd. 8, Nr. 1, S. 193–207, März 1979, doi: 10.1016/S0300-595X(79)80017-1

[20] R. O. Plail, H. J. R. Bussey, G. Glazer, und J. P. S. Thomson, „Adenomatous polyposis: An association with carcinoma of the thyroid“, *Br. J. Surg.*, Bd. 74, Nr. 5, S. 377–380, Dez. 2005, doi: 10.1002/bjs.1800740517

[21] E. Chmielik, D. Rusinek, M. Oczko-Wojciechowska, M. Jarzab, J. Krajewska, A. Czarniecka, und B. Jarzab, „Heterogeneity of Thyroid Cancer“, *Pathobiology*, Bd. 85, Nr. 1–2, S. 117–129, 2018, doi: 10.1159/000486422

[22] T. Takano, „Fetal cell carcinogenesis of the thyroid: Theory and practice“, *Semin. Cancer Biol.*, Bd. 17, Nr. 3, S. 233–240, Juni 2007, doi: 10.1016/j.semcancer.2006.02.001

[23] Y. E. Nikiforov und M. N. Nikiforova, „Molecular genetics and diagnosis of thyroid cancer“, *Nat. Rev. Endocrinol.*, Bd. 7, Nr. 10, S. 569–580, Okt. 2011, doi: 10.1038/nrendo.2011.142

[24] T. Takano, „Fetal cell carcinogenesis of the thyroid: a modified theory based on recent evidence.“, Endocr. J., Bd. 61, Nr. 4, S. 311–320, 2014, doi: 10.1507/endocrj.ej13-0517

[25] A. Sastre-Perona und P. Santisteban, „Role of the Wnt Pathway in Thyroid Cancer“, *Front. Endocrinol.*, Bd. 3, 2012, doi: 10.3389/fendo.2012.00031. http://journal.frontiersin.org/article/10.3389/fendo.2012.00031/abstract. [Jan. 18, 2022]

[26] N. Mitsutake, A. Iwao, K. Nagai, H. Namba, A. Ohtsuru, V. Saenko, und S. Yamashita, „Characterization of Side Population in Thyroid Cancer Cell Lines: Cancer Stem-Like Cells Are Enriched Partly But Not Exclusively“, *Endocrinology*, Bd. 148, Nr. 4, S. 1797–1803, Apr. 2007, doi: 10.1210/en.2006-1553

[27] K. Kasaian, S. M. Wiseman, B. A. Walker, J. E. Schein, Y. Zhao, M. Hirst, R. A. Moore, A. J. Mungall, M. A. Marra, und S. J. Jones, „The genomic and transcriptomic landscape of anaplastic thyroid cancer: implications for therapy“, *BMC Cancer*, Bd. 15, Nr. 1, S. 984, Dez. 2015, doi: 10.1186/s12885-015-1955-9

[28] I. Landa, T. Ibrahimpasic, L. Boucai, R. Sinha, J. A. Knauf, R. H. Shah, S. Dogan, J. C. Ricarte-Filho, G. P. Krishnamoorthy, B. Xu, N. Schultz, M. F. Berger, C. Sander, B. S. Taylor, R. Ghossein, I. Ganly, und J. A. Fagin, „Genomic and transcriptomic hallmarks of poorly differentiated and anaplastic thyroid cancers“, *J. Clin. Invest.*, Bd. 126, Nr. 3, S. 1052–1066, Feb. 2016, doi: 10.1172/JCI85271

[29] S. Filetti, C. Durante, D. Hartl, S. Leboulleux, L. D. Locati, K. Newbold, M. G. Papotti, und A. Berruti, „Thyroid cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up“, *Ann. Oncol.*, Bd. 30, Nr. 12, S. 1856–1883, Dez. 2019, doi: 10.1093/annonc/mdz400

[30] M. E. Cabanillas, D. G. McFadden, und C. Durante, „Thyroid cancer“, *The Lancet*, Bd. 388, Nr. 10061, S. 2783–2795, Dez. 2016, doi: 10.1016/S0140-6736(16)30172-6

[31] A. Prete, P. Borges de Souza, S. Censi, M. Muzza, N. Nucci, und M. Sponziello, „Update on Fundamental Mechanisms of Thyroid Cancer“, *Front. Endocrinol.*, Bd. 11, S. 102, März 2020, doi: 10.3389/fendo.2020.00102

[32] N. Pozdeyev, L. M. Gay, E. S. Sokol, R. Hartmaier, K. E. Deaver, S. Davis, J. D. French, P. V. Borre, D. V. LaBarbera, A.-C. Tan, R. E. Schweppe, L. Fishbein, J. S. Ross, B. R. Haugen, und D. W. Bowles, „Genetic Analysis of 779 Advanced Differentiated and Anaplastic Thyroid Cancers“, *Clin. Cancer Res.*, Bd. 24, Nr. 13, S. 3059–3068, Juli 2018, doi: 10.1158/1078-0432.CCR-18-0373

[33] A. Deeken-Draisey, G.-Y. Yang, J. Gao, und B. A. Alexiev, „Anaplastic thyroid carcinoma: an epidemiologic, histologic, immunohistochemical, and molecular single-institution study“, *Hum. Pathol.*, Bd. 82, S. 140–148, Dez. 2018, doi: 10.1016/j.humpath.2018.07.027

[34] J. Liu und R. E. Brown, „Morphoproteomics demonstrates activation of mTOR pathway in anaplastic thyroid carcinoma: a preliminary observation.“, Ann. Clin. Lab. Sci., Bd. 40, Nr. 3, S. 211–217, Sommer 2010, PMID: 20689131

[35] K. C. Bible, E. Kebebew, J. Brierley, J. P. Brito, M. E. Cabanillas, T. J. J. Clark, A. Di Cristofano, R. Foote, T. Giordano, J. Kasperbauer, K. Newbold, Y. E. Nikiforov, G. Randolph, M. S. Rosenthal, A. M. Sawka, M. Shah, A. Shaha, R. Smallridge, und C. K. Wong-Clark, „2021 American Thyroid Association Guidelines for Management of Patients with Anaplastic Thyroid Cancer.“, *Thyroid Off. J. Am. Thyroid Assoc.*, Bd. 31, Nr. 3, S. 337–386, März 2021, doi: 10.1089/thy.2020.0944

[36] M. Ragazzi, A. Ciarrocchi, V. Sancisi, G. Gandolfi, A. Bisagni, und S. Piana, „Update on Anaplastic Thyroid Carcinoma: Morphological, Molecular, and Genetic Features of the Most Aggressive Thyroid Cancer“, *Int. J. Endocrinol.*, Bd. 2014, S. 1–13, 2014, doi: 10.1155/2014/790834

[37] M. L. Carcangiu, T. Steeper, G. Zampi, und J. Rosai, „Anaplastic Thyroid Carcinoma: A Study of 70 Cases“, *Am. J. Clin. Pathol.*, Bd. 83, Nr. 2, S. 135–158, Feb. 1985, doi: 10.1093/ajcp/83.2.135

[38] I. Talbott und P. E. Wakely, „Undifferentiated (anaplastic) thyroid carcinoma: Practical immunohistochemistry and cytologic look-alikes“, *Semin. Diagn. Pathol.*, Bd. 32, Nr. 4, S. 305–310, Juli 2015, doi: 10.1053/j.semdp.2014.12.012

[39] N. G. Ordóñnez, A. K. El-Naggar, R. C. Hickey, und N. A. Samaan, „Anaplastic Thyroid Carcinoma: *Immunocytochemical Study of 32 Cases*“, *Am. J. Clin. Pathol.*, Bd. 96, Nr. 1, S. 15–24, Juli 1991, doi: 10.1093/ajcp/96.1.15

[40] I. Sugitani, A. Miyauchi, K. Sugino, T. Okamoto, A. Yoshida, und S. Suzuki, „Prognostic Factors and Treatment Outcomes for Anaplastic Thyroid Carcinoma: ATC Research Consortium of Japan Cohort Study of 677 Patients“, *World J. Surg.*, Bd. 36, Nr. 6, S. 1247–1254, Juni 2012, doi: 10.1007/s00268-012-1437-z

[41] J. Chen, J. D. Tward, D. C. Shrieve, und Y. J. Hitchcock, „Surgery and Radiotherapy Improves Survival in Patients With Anaplastic Thyroid Carcinoma: Analysis of the Surveillance, Epidemiology, and End Results 1983–2002“, *Am. J. Clin. Oncol.*, Bd. 31, Nr. 5, S. 460–464, Okt. 2008, doi: 10.1097/COC.0b013e31816a61f3

[42] E. Brignardello, N. Palestini, F. Felicetti, A. Castiglione, A. Piovesan, M. Gallo, M. Freddi,

U. Ricardi, G. Gasparri, G. Ciccone, E. Arvat, und G. Boccuzzi, „Early Surgery and Survival of Patients with Anaplastic Thyroid Carcinoma: Analysis of a Case Series Referred to a Single Institution Between 1999 and 2012“, *Thyroid*, Bd. 24, Nr. 11, S. 1600–1606, Nov. 2014, doi: 10.1089/thy.2014.0004

[43] C. Are und A. R. Shaha, „Anaplastic Thyroid Carcinoma: Biology, Pathogenesis, Prognostic Factors, and Treatment Approaches“, *Ann. Surg. Oncol.*, Bd. 13, Nr. 4, S. 453–464, Apr. 2006, doi: 10.1245/ASO.2006.05.042

[44] C. J. C. Nel, J. A. van HEERDEN, J. R. Goellner, H. Gharib, W. M. McCONAHEY, W. F. Taylor, und C. S. Grant, „Anaplastic Carcinoma of the Thyroid: A Clinicopathologic Study of 82 Cases“, *Mayo Clin. Proc.*, Bd. 60, Nr. 1, S. 51–58, Jan. 1985, doi: 10.1016/S0025-6196(12)65285-9

[45] S. M. Glaser, S. F. Mandish, B. S. Gill, G. K. Balasubramani, D. A. Clump, und S. Beriwal, „Anaplastic thyroid cancer: Prognostic factors, patterns of care, and overall survival: Anaplastic Thyroid Cancer“, *Head Neck*, Bd. 38, Nr. S1, S. E2083–E2090, Apr. 2016, doi: 10.1002/hed.24384

[46] A. R. Shaha, A. Ferlito, R. P. Owen, C. E. Silver, J. P. Rodrigo, M. Haigentz, W. M. Mendenhall, A. Rinaldo, und R. C. Smallridge, „Airway issues in anaplastic thyroid carcinoma“, *Eur. Arch. Otorhinolaryngol.*, Bd. 270, Nr. 10, S. 2579–2583, Sep. 2013, doi: 10.1007/s00405-013-2556-3

[47] R. Ranganath, M. A. Shah, und A. R. Shah, „Anaplastic thyroid cancer“, *Curr. Opin. Endocrinol. Diabetes Obes.*, Bd. 22, Nr. 5, S. 387–391, Okt. 2015, doi: 10.1097/MED.0000000000000189

[48] E. Kebebew, F. S. Greenspan, O. H. Clark, K. A. Woeber, und A. McMillan, „Anaplastic thyroid carcinoma: Treatment outcome and prognostic factors“, *Cancer*, Bd. 103, Nr. 7, S. 1330–1335, Feb. 2005, doi: 10.1002/cncr.20936

[49] J. Akaishi, K. Sugino, W. Kitagawa, M. Nagahama, K. Kameyama, K. Shimizu, K. Ito, und K. Ito, „Prognostic Factors and Treatment Outcomes of 100 Cases of Anaplastic Thyroid Carcinoma“, *Thyroid*, Bd. 21, Nr. 11, S. 1183–1189, Nov. 2011, doi: 10.1089/thy.2010.0332

[50] T. Y. Kim, K. W. Kim, T. S. Jung, J. M. Kim, S. W. Kim, K.-W. Chung, E. Y. Kim, G. Gong, Y. L. Oh, S. Y. Cho, K. H. Yi, W. B. Kim, D. J. Park, J. H. Chung, B. Y. Cho, und Y. K. Shong, „Prognostic factors for Korean patients with anaplastic thyroid carcinoma“, *Head Neck*, Bd. 29, Nr. 8, S. 765–772, Aug. 2007, doi: 10.1002/hed.20578

[51] R. I. Haddad, C. Nasr, L. Bischoff, N. L. Busaidy, D. Byrd, G. Callender, P. Dickson, Q.-Y. Duh, H. Ehya, W. Goldner, M. Haymart, C. Hoh, J. P. Hunt, A. Iagaru, F. Kandeel, P. Kopp, D. M. Lamonica, B. McIver, C. D. Raeburn, J. A. Ridge, M. D. Ringel, R. P. Scheri, J. P. Shah, R. Sippel, R. C. Smallridge, C. Sturgeon, T. N. Wang, L. J. Wirth, R. J. Wong, A. Johnson-Chilla, K. G. Hoffmann, und L. A. Gurski, „NCCN Guidelines Insights: Thyroid Carcinoma, Version 2.2018“, *J. Natl. Compr. Canc. Netw.*, Bd. 16, Nr. 12, S. 1429–1440, Dez. 2018, doi: 10.6004/jnccn.2018.0089

[52] T. Poisson, D. Deandreis, S. Leboulleux, F. Bidault, G. Bonniaud, S. Baillot, A. Aupérin, A. Al Ghuzlan, J.-P. Travagli, J. Lumbroso, E. Baudin, und M. Schlumberger, „18F-fluorodeoxyglucose positron emission tomography and computed tomography in anaplastic thyroid cancer“, *Eur. J. Nucl. Med. Mol. Imaging*, Bd. 37, Nr. 12, S. 2277–2285, Dez. 2010, doi: 10.1007/s00259-010-1570-6

[53] N. Khan, N. Oriuchi, T. Higuchi, und K. Endo, „Review of Fluorine-18-2-Fluoro-2-Deoxy-D-Glucose Positron Emission Tomography (FDG-PET) in the Follow-Up of Medullary and Anaplastic Thyroid Carcinomas“, *Cancer Control*, Bd. 12, Nr. 4, S. 254–260, Okt. 2005, doi: 10.1177/107327480501200408

[54] T. V. Bogsrud, D. Karantanis, M. A. Nathan, B. P. Mullan, G. A. Wiseman, J. L. Kasperbauer, C. C. Reading, I. D. Hay, und V. J. Lowe, „18F-FDG PET in the management of patients with anaplastic thyroid carcinoma.“, Thyroid Off. J. Am. Thyroid Assoc., Bd. 18, Nr. 7, S. 713–719, Juli 2008, doi: 10.1089/thy.2007.0350

[55] R. W. M. Giard und J. Hermans, „Use and accuracy of fine-needle aspiration cytology in histologically proven thyroid carcinoma: An audit using a national pathology database“,

Cancer, Bd. 90, Nr. 6, S. 330–334, Dez. 2000, doi: 10.1002/1097-0142(20001225)90:6<330::AID-CNCR2>3.0.CO;2-T

[56] M. Jin, J. Jakowski, und P. E. Wakely, „Undifferentiated (anaplastic) thyroid carcinoma and its mimics: a report of 59 cases“, *J. Am. Soc. Cytopathol.*, Bd. 5, Nr. 2, S. 107–115, März 2016, doi: 10.1016/j.jasc.2015.08.001

[57] R. I. Haddad, L. Bischoff, D. Ball, V. Bernet, E. Blomain, N. L. Busaidy, M. Campbell, P. Dickson, Q.-Y. Duh, H. Ehya, W. S. Goldner, T. Guo, M. Haymart, S. Holt, J. P. Hunt, A. Iagaru, F. Kandeel, D. M. Lamonica, S. Mandel, S. Markovina, B. McIver, C. D. Raeburn, R. Rezaee, J. A. Ridge, M. Y. Roth, R. P. Scheri, J. P. Shah, J. A. Sipos, R. Sippel, C. Sturgeon, T. N. Wang, L. J. Wirth, R. J. Wong, M. Yeh, C. J. Cassara, und S. Darlow, „Thyroid Carcinoma, Version 2.2022, NCCN Clinical Practice Guidelines in Oncology“, *J. Natl. Compr. Canc. Netw.*, Bd. 20, Nr. 8, S. 925–951, Aug. 2022, doi: 10.6004/jnccn.2022.0040

[58] J. D. Brierley, M. K. Gospodarowicz, und C. Wittekind, *UICC TNM Classification of Malignant Tumours, 8th edition*. Oxford: John Wiley & Sons Inc., 2016.

[59] P. Goffredo, S. M. Thomas, M. A. Adam, J. A. Sosa, und S. A. Roman, „Impact of Timeliness of Resection and Thyroidectomy Margin Status on Survival for Patients with Anaplastic Thyroid Cancer: An Analysis of 335 Cases“, *Ann. Surg. Oncol.*, Bd. 22, Nr. 13, S. 4166–4174, Dez. 2015, doi: 10.1245/s10434-015-4742-6

[60] T.-R. Liu, Z.-W. Xiao, H.-N. Xu, Z. Long, F.-Q. Wei, S.-M. Zhuang, X.-M. Sun, L.-E. Xie, J.-S. Mu, A.-K. Yang, G.-P. Zhang, und Y. Fan, „Treatment and Prognosis of Anaplastic Thyroid Carcinoma: A Clinical Study of 50 Cases“, *PLOS ONE*, Bd. 11, Nr. 10, S. e0164840, Okt. 2016, doi: 10.1371/journal.pone.0164840

[61] Z. A. T. Aslan, M. Granados-García, K. Luna-Ortiz, F. J. Guerrero-Huerta, A. Gómez-Pedraza, S. A. Namendys-Silva, A. Meneses-García, und J. M. Ordoñez-Mosquera, „Anaplastic thyroid cancer: multimodal treatment results.“, Ecancermedicalscience, Bd. 8, S. 449, 2014, doi: 10.3332/ecancer.2014.449

[62] B. Roche, G. Larroumets, C. Dejax, F. Kwiatkowsi, F. Desbiez, P. Thieblot, und I. Tauveron, „Epidemiology, clinical presentation, treatment and prognosis of a regional series of 26 anaplastic thyroid carcinomas (ATC). Comparison with the literature“, *Ann. Endocrinol.*, Bd. 71, Nr. 1, S. 38–45, Feb. 2010, doi: 10.1016/j.ando.2009.10.013

[63] T. A. Pezzi, A. S. R. Mohamed, T. Sheu, P. Blanchard, V. C. Sandulache, S. Y. Lai, M. E. Cabanillas, M. D. Williams, C. M. Pezzi, C. Lu, A. S. Garden, W. H. Morrison, D. I. Rosenthal, C. D. Fuller, und G. B. Gunn, „Radiation therapy dose is associated with improved survival for unresected anaplastic thyroid carcinoma: Outcomes from the National Cancer Data Base: Unresected Anaplastic Thyroid Carcinoma“, *Cancer*, Bd. 123, Nr. 9, S. 1653–1661, Mai 2017, doi: 10.1002/cncr.30493

[64] V. Zivaljevic, K. Tausanovic, I. Paunovic, A. Diklic, N. Kalezic, G. Zoric, V. Sabljak, B. Vekic, R. Zivic, J. Marinkovic, und S. Sipetic, „Age as a Prognostic Factor in Anaplastic Thyroid Cancer“, *Int. J. Endocrinol.*, Bd. 2014, S. 1–5, 2014, doi: 10.1155/2014/240513

[65] I. R. Paunovic, S. B. Sipetic, G. V. Zoric, A. D. Diklic, D. V. Savic, J. Marinkovic, und V. R. Zivaljevic, „Survival and Prognostic Factors of Anaplastic Thyroid Carcinoma“, *Acta Chir. Belg.*, Bd. 115, Nr. 1, S. 62–67, Jan. 2015, doi: 10.1080/00015458.2015.11681068

[66] S.-K. Baek, M.-C. Lee, J. H. Hah, S.-H. Ahn, Y.-I. Son, Y.-S. Rho, P.-S. Chung, Y.-S. Lee, B. S. Koo, K.-Y. Jung, und B.-J. Lee, „Role of surgery in the management of anaplastic thyroid carcinoma: Korean nationwide multicenter study of 329 patients with anaplastic thyroid carcinoma, 2000 to 2012: Surgical role in anaplastic thyroid carcinoma“, *Head Neck*, Bd. 39, Nr. 1, S. 133–139, Jan. 2017, doi: 10.1002/hed.24559

[67] M. de Ridder, E. Nieveen van Dijkum, A. Engelsman, E. Kapiteijn, H.-J. Klümpen, und C. R. N. Rasch, „Anaplastic thyroid carcinoma: a nationwide cohort study on incidence, treatment and survival in the Netherlands over 3 decades“, *Eur. J. Endocrinol.*, Bd. 183, Nr. 2, S. 203–209, Aug. 2020, doi: 10.1530/EJE-20-0080

[68] W. Gui, W. Zhu, W. Lu, C. Shang, F. Zheng, X. Lin, und H. Li, „Development and validation of a prognostic nomogram to predict overall survival and cancer-specific survival for patients with anaplastic thyroid carcinoma“, *PeerJ*, Bd. 8, S. e9173, Mai 2020, doi:

10.7717/peerj.9173

[69] N. Huang, X. Shi, B. Lei, W. Wei, Z. Lu, P. Yu, Y. Wang, Q. Ji, und Y. Wang, „An Update of the Appropriate Treatment Strategies in Anaplastic Thyroid Cancer: A Population-Based Study of 735 Patients“, *Int. J. Endocrinol.*, Bd. 2019, S. 1–7, Feb. 2019, doi: 10.1155/2019/8428547

[70] D. Fan, J. Ma, A. C. Bell, A. H. Groen, K. S. Olsen, B. H. Lok, J. E. Leeman, E. Anderson, N. Riaz, S. McBride, I. Ganly, A. R. Shaha, E. J. Sherman, C. J. Tsai, J. J. Kang, und N. Y. Lee, „Outcomes of multimodal therapy in a large series of patients with anaplastic thyroid cancer“, *Cancer*, Bd. 126, Nr. 2, S. 444–452, Jan. 2020, doi: 10.1002/cncr.32548

[71] T. Higashiyama, Y. Ito, M. Hirokawa, M. Fukushima, T. Uruno, A. Miya, F. Matsuzuka, und A. Miyauchi, „Induction Chemotherapy with Weekly Paclitaxel Administration for Anaplastic Thyroid Carcinoma“, *Thyroid*, Bd. 20, Nr. 1, S. 7–14, Jan. 2010, doi: 10.1089/thy.2009.0115

[72] N. Onoda, K. Sugino, T. Higashiyama, M. Kammori, K. Toda, K. Ito, A. Yoshida, N. Suganuma, N. Nakashima, S. Suzuki, K. Tsukahara, H. Noguchi, M. Koizumi, T. Nemoto, H. Hara, A. Miyauchi, und I. Sugitani, „The Safety and Efficacy of Weekly Paclitaxel Administration for Anaplastic Thyroid Cancer Patients: A Nationwide Prospective Study“, *Thyroid*, Bd. 26, Nr. 9, S. 1293–1299, Sep. 2016, doi: 10.1089/thy.2016.0072

[73] J. Tennvall, G. Lundell, P. Wahlberg, A. Bergenfelz, L. Grimelius, M. Åkerman, A.-L. Hjelm Skog, und G. Wallin, „Anaplastic thyroid carcinoma: three protocols combining doxorubicin, hyperfractionated radiotherapy and surgery“, *Br. J. Cancer*, Bd. 86, Nr. 12, S. 1848–1853, Juni 2002, doi: 10.1038/sj.bjc.6600361

[74] N. Besic, M. Auersperg, M. Us-Krasovec, R. Golouh, S. Frkovic-Grazio, und A. Vodnik, „Effect of primary treatment on survival in anaplastic thyroid carcinoma“, *Eur. J. Surg. Oncol. EJSO*, Bd. 27, Nr. 3, S. 260–264, Apr. 2001, doi: 10.1053/ejso.2000.1098

[75] V. Subbiah, R. J. Kreitman, Z. A. Wainberg, J. Y. Cho, J. H. M. Schellens, J. C. Soria, P. Y. Wen, C. Zielinski, M. E. Cabanillas, G. Urbanowitz, B. Mookerjee, D. Wang, F. Rangwala, und B. Keam, „Dabrafenib and Trametinib Treatment in Patients With Locally Advanced or Metastatic *BRAF* V600–Mutant Anaplastic Thyroid Cancer“, *J. Clin. Oncol.*, Bd. 36, Nr. 1, S. 7–13, Jan. 2018, doi: 10.1200/JCO.2017.73.6785

[76] A. Drilon, T. W. Laetsch, S. Kummar, S. G. DuBois, U. N. Lassen, G. D. Demetri, M. Nathenson, R. C. Doebele, A. F. Farago, A. S. Pappo, B. Turpin, A. Dowlati, M. S. Brose, L. Mascarenhas, N. Federman, J. Berlin, W. S. El-Deiry, C. Baik, J. Deeken, V. Boni, R. Nagasubramanian, M. Taylor, E. R. Rudzinski, F. Meric-Bernstam, D. P. S. Sohal, P. C. Ma, L. E. Raez, J. F. Hechtman, R. Benayed, M. Ladanyi, B. B. Tuch, K. Ebata, S. Cruickshank, N. C. Ku, M. C. Cox, D. S. Hawkins, D. S. Hong, und D. M. Hyman, „Efficacy of Larotrectinib in *TRK* Fusion–Positive Cancers in Adults and Children“, *N. Engl. J. Med.*, Bd. 378, Nr. 8, S. 731–739, Feb. 2018, doi: 10.1056/NEJMoa1714448

[77] L. J. Wirth, E. Sherman, B. Robinson, B. Solomon, H. Kang, J. Lorch, F. Worden, M. Brose, J. Patel, S. Leboulleux, Y. Godbert, F. Barlesi, J. C. Morris, T. K. Owonikoko, D. S. W. Tan, O. Gautschi, J. Weiss, C. de la Fouchardière, M. E. Burkard, J. Laskin, M. H. Taylor, M. Kroiss, J. Medioni, J. W. Goldman, T. M. Bauer, B. Levy, V. W. Zhu, N. Lakhani, V. Moreno, K. Ebata, M. Nguyen, D. Heirich, E. Y. Zhu, X. Huang, L. Yang, J. Kherani, S. M. Rothenberg, A. Drilon, V. Subbiah, M. H. Shah, und M. E. Cabanillas, „Efficacy of Selpercatinib in *RET* -Altered Thyroid Cancers“, *N. Engl. J. Med.*, Bd. 383, Nr. 9, S. 825–835, Aug. 2020, doi: 10.1056/NEJMoa2005651

[78] Y. Godbert, B. Henriques de Figueiredo, F. Bonichon, F. Chibon, I. Hostein, G. Pérot, C. Dupin, A. Daubech, G. Belleannée, A. Gros, A. Italiano, und I. Soubeyran, „Remarkable Response to Crizotinib in Woman With Anaplastic Lymphoma Kinase–Rearranged Anaplastic Thyroid Carcinoma“, *J. Clin. Oncol.*, Bd. 33, Nr. 20, S. e84–e87, Juli 2015, doi: 10.1200/JCO.2013.49.6596

[79] A. Hatashima, B. Archambeau, H. Armbruster, M. Xu, M. Shah, B. Konda, A. Lott Limbach, und V. Sukrithan, „An Evaluation of Clinical Efficacy of Immune Checkpoint Inhibitors for Patients with Anaplastic Thyroid Carcinoma“, *Thyroid*, Bd. 32, Nr. 8, S. 926–936, Aug. 2022, doi: 10.1089/thy.2022.0073

[80] C. Dierks, J. Seufert, K. Aumann, J. Ruf, C. Klein, S. Kiefer, M. Rassner, M. Boerries, A. Zielke, P. la Rosee, P. T. Meyer, M. Kroiss, C. Weißenberger, T. Schumacher, P. Metzger, H. Weiss, C. Smaxwil, K. Laubner, J. Duyster, N. von Bubnoff, C. Miething, und O. Thomusch, „Combination of Lenvatinib and Pembrolizumab Is an Effective Treatment Option for Anaplastic and Poorly Differentiated Thyroid Carcinoma“, *Thyroid*, Bd. 31, Nr. 7, S. 1076–1085, Juli 2021, doi: 10.1089/thy.2020.0322

[81] P. C. Iyer, R. Dadu, M. Gule-Monroe, N. L. Busaidy, R. Ferrarotto, M. A. Habra, M. Zafereo, M. D. Williams, G. B. Gunn, H. Grosu, H. D. Skinner, E. M. Sturgis, N. Gross, und M. E. Cabanillas, „Salvage pembrolizumab added to kinase inhibitor therapy for the treatment of anaplastic thyroid carcinoma“, *J. Immunother. Cancer*, Bd. 6, Nr. 1, S. 68, Dez. 2018, doi: 10.1186/s40425-018-0378-y

[82] A. M. Goodman, S. Kato, L. Bazhenova, S. P. Patel, G. M. Frampton, V. Miller, P. J. Stephens, G. A. Daniels, und R. Kurzrock, „Tumor Mutational Burden as an Independent Predictor of Response to Immunotherapy in Diverse Cancers“, *Mol. Cancer Ther.*, Bd. 16, Nr. 11, S. 2598–2608, Nov. 2017, doi: 10.1158/1535-7163.MCT-17-0386

[83] G. Lin, X. Fan, W. Zhu, C. Huang, W. Zhuang, H. Xu, X. Lin, D. Hu, Y. Huang, K. Jiang, Q. Miao, und C. Li, „Prognostic significance of PD-L1 expression and tumor infiltrating lymphocyte in surgically resectable non-small cell lung cancer“, *Oncotarget*, Bd. 8, Nr. 48, S. 83986–83994, Okt. 2017, doi: 10.18632/oncotarget.20233

[84] L. J. Wirth, E. Eigendorff, J. Capdevila, L. G. Paz-Ares, C.-C. Lin, M. H. Taylor, R. Ramlau, M. Butler, J.-P. Delord, Z. Horvath, H. Gelderblom, P. A. Ascierto, A. Fasolo, D. Führer, H. Wu, G. Bostel, S. Cameron, J. E. Faris, und A. I. Varga, „Phase I/II study of spartalizumab (PDR001), an anti-PD1 mAb, in patients with anaplastic thyroid cancer.“, *J. Clin. Oncol.*, Bd. 36, Nr. 15_suppl, S. 6024–6024, Mai 2018, doi: 10.1200/JCO.2018.36.15_suppl.6024

[85] M. E. Cabanillas, R. Ferrarotto, A. S. Garden, S. Ahmed, N. L. Busaidy, R. Dadu, M. D. Williams, H. Skinner, G. B. Gunn, H. Grosu, P. Iyer, M. C. Hofmann, und M. Zafereo, „Neoadjuvant BRAF- and Immune-Directed Therapy for Anaplastic Thyroid Carcinoma“, *Thyroid*, Bd. 28, Nr. 7, S. 945–951, Juli 2018, doi: 10.1089/thy.2018.0060

[86] M. E. Cabanillas, R. Ferrarotto, A. S. Garden, S. Ahmed, N. L. Busaidy, R. Dadu, M. D. Williams, H. Skinner, G. B. Gunn, H. Grosu, P. Iyer, M. C. Hofmann, und M. Zafereo, „Neoadjuvant BRAF- and Immune-Directed Therapy for Anaplastic Thyroid Carcinoma“, Thyroid, Bd. 28, Nr. 7, S. 945–951, Juli 2018, doi: 10.1089/thy.2018.0060

[87] M. E. Cabanillas (Leiter der Studie [principal investigator]), „Lenvatinib and Pembrolizumab for the Treatment of Stage IVB Locally Advanced and Unresectable or Stage IVC Metastatic Anaplastic Thyroid Cancer“, ClinicalTrials.gov, National Library of Medicine, Update Juli 21, 2023. https://clinicaltrials.gov/study/NCT04171622. [zugegriffen Apr. 26, 2024]

[87] M. Zafereo (Leiter der Studie [principal investigator]), „Pembrolizumab, Dabrafenib, and Trametinib Before Surgery for the Treatment of BRAF-Mutated Anaplastic Thyroid Cancer“, ClinicalTrials.gov, National Library of Medicine, Update Apr. 17, 2024. https://clinicaltrials.gov/study/NCT04675710. [zugegriffen Apr. 26, 2024]

[88] N. Y. Lee, N. Riaz, V. Wu, T. Brinkman, C. J. Tsai, W. Zhi, J. Fetten, A. Ho, R. J. Wong, R. Ghossein, M. Tuttle, J. Fagin, D. G. Pfister, und E. Sherman, „A Pilot Study of Durvalumab (MEDI4736) with Tremelimumab in Combination with Image-Guided Stereotactic Body Radiotherapy in the Treatment of Metastatic Anaplastic Thyroid Cancer“, Thyroid, Bd. 32, Nr. 7, S. 799–806, Juli 2022, doi: 10.1089/thy.2022.0050

[89] E. J. Sherman, J. Harris, K. C. Bible, P. Xia, R. A. Ghossein, C. H. Chung, N. Riaz, G. B. Gunn, R. L. Foote, S. S. Yom, S. J. Wong, S. A. Koyfman, M. F. Dzeda, D. A. Clump, S. A. Khan, M. H. Shah, K. Redmond, P. A. Torres-Saavedra, Q.-T. Le, und N. Y. Lee, „Radiotherapy and paclitaxel plus pazopanib or placebo in anaplastic thyroid cancer (NRG/RTOG 0912): a randomised, double-blind, placebo-controlled, multicentre, phase 2 trial“, Lancet Oncol., Bd. 24, Nr. 2, S. 175–186, Feb. 2023, doi: 10.1016/S1470-2045(22)00763-X

[90] E. J. Sherman (Leiter der Studie [principal investigator]), „Study of Cemiplimab Combined With Dabrafenib and Trametinib in People With Anaplastic Thyroid Cancer“, ClinicalTri-

als.gov, National Library of Medicine, Update Juli 03, 2023. https://clinicaltrials.gov/study/NCT04238624. [zugegriffen Apr. 26, 2024]

[91] S. Fazeli (Leiter der Studie [principal investigator]), „Dabrafenib, Trametinib, and IMRT in Treating Patients With BRAF Mutated Anaplastic Thyroid Cancer“, ClinicalTrials.gov, National Library of Medicine, Update Okt. 10, 2023. https://clinicaltrials.gov/study/NCT03975231. [zugegriffen Apr. 26, 2024]

[92] S. A. Khan (Leiter der Studie [principal investigator]), „Phase II Trial of Pembrolizumab in Metastatic or Locally Advanced Anaplastic/Undifferentiated Thyroid Cancer“, ClinicalTrials.gov, National Library of Medicine, Update Nov. 11, 2021. https://clinicaltrials.gov/study/NCT05119296. [zugegriffen Apr. 26, 2024]

[93] M. E. Cabanillas (Leiter der Studie [principal investigator]), „Atezolizumab With Chemotherapy in Treating Patients With Anaplastic or Poorly Differentiated Thyroid Cancer“, ClinicalTrials.gov, National Library of Medicine, Update Dez. 07, 2023. https://clinicaltrials.gov/study/NCT03181100. [zugegriffen Apr. 26, 2024]

[94] N. Prasongsook, A. Kumar, A. V. Chintakuntlawar, R. L. Foote, J. Kasperbauer, J. Molina, Y. Garces, D. Ma, M. A. N. Wittich, J. Rubin, R. Richardson, J. Morris, I. Hay, V. Fatourechi, B. McIver, M. Ryder, G. Thompson, C. Grant, M. Richards, T. J. Sebo, M. Rivera, V. Suman, S. M. Jenkins, R. C. Smallridge, und K. C. Bible, „Survival in Response to Multimodal Therapy in Anaplastic Thyroid Cancer“, *J. Clin. Endocrinol. Metab.*, Bd. 102, Nr. 12, S. 4506–4514, Dez. 2017, doi: 10.1210/jc.2017-01180

[95] K. Ito, T. Hanamura, K. Murayama, T. Okada, T. Watanabe, M. Harada, T. Ito, H. Koyama, T. Kanai, K. Maeno, Y. Mochizuki, und J. Amano, „Multimodality therapeutic outcomes In anaplastic thyroid carcinoma: Improved survival in subgroups of patients with localized primary tumors“, *Head Neck*, Bd. 34, Nr. 2, S. 230–237, Feb. 2012, doi: 10.1002/hed.21721

[96] B. Busnardo, O. Daniele, M. R. Pelizzo, R. Mazzarotto, D. Nacamulli, D. DeVido, C. Mian, und M. E. Girelli, „A multimodality therapeutic approach in anaplastic thyroid carcinoma: Study on 39 patients“, *J. Endocrinol. Invest.*, Bd. 23, Nr. 11, S. 755–761, Dez. 2000, doi: 10.1007/BF03345066

[97] P. I. Haigh, P. H. G. Ituarte, H. S. Wu, P. A. Treseler, M. D. Posner, J. M. Quivey, Q. Y. Duh, und O. H. Clark, „Completely resected anaplastic thyroid carcinoma combined with adjuvant chemotherapy and irradiation is associated with prolonged survival“, *Cancer*, Bd. 91, Nr. 12, S. 2335–2342, Juni 2001, doi: 10.1002/1097-0142(20010615)91:12<2335::AID-CNCR1266>3.0.CO;2-1

[98] A. T. Swaak-Kragten, J. H. W. de Wilt, P. I. M. Schmitz, M. Bontenbal, und P. C. Levendag, „Multimodality treatment for anaplastic thyroid carcinoma – Treatment outcome in 75 patients“, *Radiother. Oncol.*, Bd. 92, Nr. 1, S. 100–104, Juli 2009, doi: 10.1016/j.radonc.2009.02.016

[99] D. Y. Lee, J.-K. Won, S.-H. Lee, D. J. Park, K. C. Jung, M.-W. Sung, H.-G. Wu, K. H. Kim, Y. J. Park, und J. H. Hah, „Changes of Clinicopathologic Characteristics and Survival Outcomes of Anaplastic and Poorly Differentiated Thyroid Carcinoma“, *Thyroid*, Bd. 26, Nr. 3, S. 404–413, März 2016, doi: 10.1089/thy.2015.0316

[100] Th. Hölting, H. Meybier, und H. Buhr, „Probleme der Tracheotomie beim organüberschreitenden anaplastischen Schilddrüsencarcinom“, *Langenbecks Arch. Für Chir.*, Bd. 374, Nr. 2, S. 72–76, März 1989, doi: 10.1007/BF01261613

[101] N. Mani, K. McNamara, N. Lowe, S. Loughran, und B. K. Yap, „Management of the compromised airway and role of tracheotomy in anaplastic thyroid carcinoma: Management of the compromised airway in anaplastic thyroid cancer“, *Head Neck*, Bd. 38, Nr. 1, S. 85–88, Jan. 2016, doi: 10.1002/hed.23857

[102] D. Gilony, D. Gilboa, T. Blumstein, H. Murad, Y. P. Talmi, J. Kronenberg, und M. Wolf, „Effects of Tracheostomy on Well-being and Body-Image Perceptions“, *Otolaryngol. Neck Surg.*, Bd. 133, Nr. 3, S. 366–371, Sep. 2005, doi: 10.1016/j.otohns.2005.04.025

[103] V. Tiedje, M. Stuschke, F. Weber, H. Dralle, L. Moss, und D. Führer, „Anaplastic thyroid carcinoma: review of treatment protocols“, *Endocr. Relat. Cancer*, Bd. 25, Nr. 3, S. R153–R161, März 2018, doi: 10.1530/ERC-17-0435

[104] E. J. Sherman, S. H. Lim, A. L. Ho, R. A. Ghossein, M. G. Fury, A. R. Shaha, M. Rivera, O. Lin, S. Wolden, N. Y. Lee, und D. G. Pfister, „Concurrent doxorubicin and radiotherapy for anaplastic thyroid cancer: A critical re-evaluation including uniform pathologic review“, *Radiother. Oncol.*, Bd. 101, Nr. 3, S. 425–430, Dez. 2011, doi: 10.1016/j.radonc.2011.09.004

[105] A. E. Nahum, „The Radiobiology of Hypofractionation“, *Clin. Oncol.*, Bd. 27, Nr. 5, S. 260–269, Mai 2015, doi: 10.1016/j.clon.2015.02.001

[106] P. Perros, K. Boelaert, S. Colley, C. Evans, R. M. Evans, G. Gerrard BA, J. Gilbert, B. Harrison, S. J. Johnson, T. E. Giles, L. Moss, V. Lewington, K. Newbold, J. Taylor, R. V. Thakker, J. Watkinson, und G. R. Williams, „Guidelines for the management of thyroid cancer“, *Clin. Endocrinol. (Oxf.)*, Bd. 81, S. 1–122, Juli 2014, doi: 10.1111/cen.12515

[107] S. J. McMahon, „The linear quadratic model: usage, interpretation and challenges“, *Phys. Med. Biol.*, Bd. 64, Nr. 1, S. 01TR01, Dez. 2018, doi: 10.1088/1361-6560/aaf26a

[108] C. M. van Leeuwen, A. L. Oei, J. Crezee, A. Bel, N. A. P. Franken, L. J. A. Stalpers, und H. P. Kok, „The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies“, *Radiat. Oncol.*, Bd. 13, Nr. 1, S. 96, Dez. 2018, doi: 10.1186/s13014-018-1040-z

[109] M. V. Williams, J. Denekamp, und J. F. Fowler, „A review of αβ ratios for experimental tumors: Implications for clinical studies of altered fractionation“, *Henry Kaplan Meml. Part 1*, Bd. 11, Nr. 1, S. 87–96, Jan. 1985, doi: 10.1016/0360-3016(85)90366-9

[110] J. F. Fowler, „The linear-quadratic formula and progress in fractionated radiotherapy“, *Br. J. Radiol.*, Bd. 62, Nr. 740, S. 679–694, Aug. 1989, doi: 10.1259/0007-1285-62-740-679

[111] R. Miralbell, S. A. Roberts, E. Zubizarreta, und J. H. Hendry, „Dose-Fractionation Sensitivity of Prostate Cancer Deduced From Radiotherapy Outcomes of 5,969 Patients in Seven International Institutional Datasets: α/β = 1.4 (0.9–2.2) Gy“, *Int. J. Radiat. Oncol.*, Bd. 82, Nr. 1, S. e17–e24, Jan. 2012, doi: 10.1016/j.ijrobp.2010.10.075

[112] N.-S. Hegemann, M. Guckenberger, C. Belka, U. Ganswindt, F. Manapov, und M. Li, „Hypofractionated radiotherapy for prostate cancer.“, *Radiat. Oncol. Lond. Engl.*, Bd. 9, S. 275, Dez. 2014, doi: 10.1186/s13014-014-0275-6

[113] D. T. Chang, R. J. Amdur, C. G. Morris, und W. M. Mendenhall, „Adjuvant radiotherapy for cutaneous melanoma: Comparing hypofractionation to conventional fractionation“, *Int. J. Radiat. Oncol.*, Bd. 66, Nr. 4, S. 1051–1055, Nov. 2006, doi: 10.1016/j.ijrobp.2006.05.056

[114] J. J. Caudell, M. C. Ward, N. Riaz, S. J. Zakem, M. J. Awan, N. E. Dunlap, D. Isrow, C. Hassanzadeh, J. A. Vargo, D. E. Heron, S. Marcrom, D. H. Boggs, C. A. Reddy, J. Dault, J. A. Bonner, K. A. Higgins, J. J. Beitler, S. A. Koyfman, M. Machtay, M. Yao, A. M. Trotti, F. Siddiqui, und N. Y. Lee, „Volume, Dose, and Fractionation Considerations for IMRT-based Reirradiation in Head and Neck Cancer: A Multi-institution Analysis“, *Int. J. Radiat. Oncol.*, Bd. 100, Nr. 3, S. 606–617, März 2018, doi: 10.1016/j.ijrobp.2017.11.036

[115] H. Koseła-Paterczyk, M. Szacht, T. Morysiński, I. Ługowska, W. Dziewirski, S. Falkowski, M. Zdzienicki, A. Pieńkowski, K. Szamotulska, T. Świtaj, und P. Rutkowski, „Preoperative hypofractionated radiotherapy in the treatment of localized soft tissue sarcomas“, *Eur. J. Surg. Oncol. EJSO*, Bd. 40, Nr. 12, S. 1641–1647, Dez. 2014, doi: 10.1016/j.ejso.2014.05.016

[116] A. Oweida, A. Phan, B. Vancourt, T. Robin, M. K. Hararah, S. Bhatia, D. Milner, S. Lennon, L. Pike, D. Raben, B. Haugen, N. Pozdeyev, R. Schweppe, und S. D. Karam, „Hypofractionated Radiotherapy Is Superior to Conventional Fractionation in an Orthotopic Model of Anaplastic Thyroid Cancer“, *Thyroid*, Bd. 28, Nr. 6, S. 739–747, Juni 2018, doi: 10.1089/thy.2017.0706

[117] T. Yang, H. Namba, T. Hara, N. Takmura, Y. Nagayama, S. Fukata, N. Ishikawa, K. Kuma, K. Ito, und S. Yamashita, „p53 induced by ionizing radiation mediates DNA end-jointing activity, but not apoptosis of thryroid cells“, *Oncogene*, Bd. 14, Nr. 13, S. 1511–1519, Apr. 1997, doi: 10.1038/sj.onc.1200979

[118] H. Namba, T. Hara, T. Tukazaki, K. Migita, N. Ishikawa, K. Ito, S. Nagataki, und S. Yamashita, „Radiation-induced G1 Arrest Is Selectively Mediated by the p53-WAF1/Cip1 Pathway in Human Thyroid Cells1“, *Cancer Res.*, Bd. 55, Nr. 10, S. 2075–2080, Mai 1995, PMID: 7743505

[119] I. Shuryak, E. J. Hall, und D. J. Brenner, „Optimized Hypofractionation Can Markedly Improve Tumor Control and Decrease Late Effects for Head and Neck Cancer“, *Int. J. Radiat. Oncol.*, Bd. 104, Nr. 2, S. 272–278, Juni 2019, doi: 10.1016/j.ijrobp.2019.02.025

[120] A.-K. Dumke, T. Pelz, und D. Vordermark, „Long-term results of radiotherapy in anaplastic thyroid cancer“, *Radiat. Oncol.*, Bd. 9, Nr. 1, S. 90, Dez. 2014, doi: 10.1186/1748-717X-9-90

[121] N. Takahashi, H. Matsushita, R. Umezawa, T. Yamamoto, Y. Ishikawa, Y. Katagiri, S. Tasaka, K. Takeda, K. Fukui, N. Kadoya, K. Ito, und K. Jingu, „Hypofractionated Radiotherapy for Anaplastic Thyroid Carcinoma: 15 Years of Experience in a Single Institution“, *Eur. Thyroid J.*, Bd. 8, Nr. 1, S. 24–30, 2019, doi: 10.1159/000493315

[122] K. So, R. E. Smith, und S. R. Davis, „Radiotherapy in anaplastic thyroid carcinoma: An Australian experience“, *J. Med. Imaging Radiat. Oncol.*, Bd. 61, Nr. 2, S. 279–287, Apr. 2017, doi: 10.1111/1754-9485.12552

[123] M. J. Stavas, E. T. Shinohara, A. Attia, M. S. Ning, J. M. Friedman, und A. J. Cmelak, „Short Course High Dose Radiotherapy in the Treatment of Anaplastic Thyroid Carcinoma“, *J. Thyroid Res.*, Bd. 2014, S. 1–7, 2014, doi: 10.1155/2014/764281

[124] Y. Nachalon, S. Stern-Shavit, G. Bachar, J. Shvero, D. Limon, und A. Popovtzer, „Aggressive Palliation and Survival in Anaplastic Thyroid Carcinoma“, *JAMA Otolaryngol. Neck Surg.*, Bd. 141, Nr. 12, S. 1128, Dez. 2015, doi: 10.1001/jamaoto.2015.2332

[125] M. E. Salive, „Multimorbidity in Older Adults“, *Epidemiol. Rev.*, Bd. 35, Nr. 1, S. 75–83, Jan. 2013, doi: 10.1093/epirev/mxs009

[126] J. L. Wolff, B. Starfield, und G. Anderson, „Prevalence, Expenditures, and Complications of Multiple Chronic Conditions in the Elderly“, *Arch. Intern. Med.*, Bd. 162, Nr. 20, S. 2269, Nov. 2002, doi: 10.1001/archinte.162.20.2269

[127] K. P. Loh, E. Soto-Perez-de-Celis, T. Hsu, N. A. de Glas, N. M. L. Battisti, C. Baldini, M. Rodrigues, S. M. Lichtman, und H. Wildiers, „What Every Oncologist Should Know About Geriatric Assessment for Older Patients With Cancer: Young International Society of Geriatric Oncology Position Paper“, *J. Oncol. Pract.*, Bd. 14, Nr. 2, S. 85–94, Feb. 2018, doi: 10.1200/JOP.2017.026435

[128] A.-C. Scharf, J. Gronewold, C. Dahlmann, J. Schlitzer, A. Kribben, G. Gerken, H. Frohnhofen, R. Dodel, und D. M. Hermann, „Clinical and functional patient characteristics predict medical needs in older patients at risk of functional decline“, *BMC Geriatr.*, Bd. 20, Nr. 1, S. 75, Dez. 2020, doi: 10.1186/s12877-020-1443-1

[129] R. J. Van Marum, „Underrepresentation of the elderly in clinical trials, time for action“, *Br. J. Clin. Pharmacol.*, Bd. 86, Nr. 10, S. 2014–2016, Okt. 2020, doi: 10.1111/bcp.14539

[130] I. Sugitani, N. Onoda, K. Ito, und S. Suzuki, „Management of Anaplastic Thyroid Carcinoma: the Fruits from the ATC Research Consortium of Japan“, *J. Nippon Med. Sch.*, Bd. 85, Nr. 1, S. 18–27, 2018, doi: 10.1272/jnms.2018_85-3

[131] M. R. Haymart, M. Banerjee, H. Yin, F. Worden, und J. J. Griggs, „Marginal treatment benefit in anaplastic thyroid cancer: Treatment of Anaplastic Thyroid Cancer“, *Cancer*, Bd. 119, Nr. 17, S. 3133–3139, Sep. 2013, doi: 10.1002/cncr.28187

[132] K. L. Corrigan, H. Williamson, D. Elliott Range, D. Niedzwiecki, D. M. Brizel, und Y. M. Mowery, „Treatment Outcomes in Anaplastic Thyroid Cancer“, *J. Thyroid Res.*, Bd. 2019, S. 1–11, Mai 2019, doi: 10.1155/2019/8218949

[133] J. Wendler, M. Kroiss, K. Gast, M. C. Kreissl, S. Allelein, U. Lichtenauer, R. Blaser, C. Spitzweg, M. Fassnacht, M. Schott, D. Führer, und V. Tiedje, „Clinical presentation, treatment and outcome of anaplastic thyroid carcinoma: results of a multicenter study in Germany“, *Eur. J. Endocrinol.*, Bd. 175, Nr. 6, S. 521–529, Dez. 2016, doi: 10.1530/EJE-16-0574

[134] S. Wächter, A. Wunderlich, S. Roth, I. Mintziras, E. Maurer, S. Hoffmann, F. Verburg, S. Fellinger, K. Holzer, D. Bartsch, und P. Di Fazio, „Individualised Multimodal Treatment Strategies for Anaplastic and Poorly Differentiated Thyroid Cancer“, *J. Clin. Med.*, Bd. 7, Nr. 5, S. 115, Mai 2018, doi: 10.3390/jcm7050115

[135] S. M. Lim, S.-J. Shin, W. Y. Chung, C. S. Park, K.-H. Nam, S.-W. Kang, K. C. Keum, J. H. Kim, J. Y. Cho, Y. K. Hong, und B. C. Cho, „Treatment Outcome of Patients with Anaplastic Thyroid Cancer: A Single Center Experience“, *Yonsei Med. J.*, Bd. 53, Nr. 2, S. 352, 2012, doi: 10.3349/ymj.2012.53.2.352

[136] R. De Crevoisier, E. Baudin, A. Bachelot, S. Leboulleux, J.-P. Travagli, B. Caillou, und M. Schlumberger, „Combined treatment of anaplastic thyroid carcinoma with surgery, chemotherapy, and hyperfractionated accelerated external radiotherapy“, *Int. J. Radiat. Oncol.*, Bd. 60, Nr. 4, S. 1137–1143, Nov. 2004, doi: 10.1016/j.ijrobp.2004.05.032

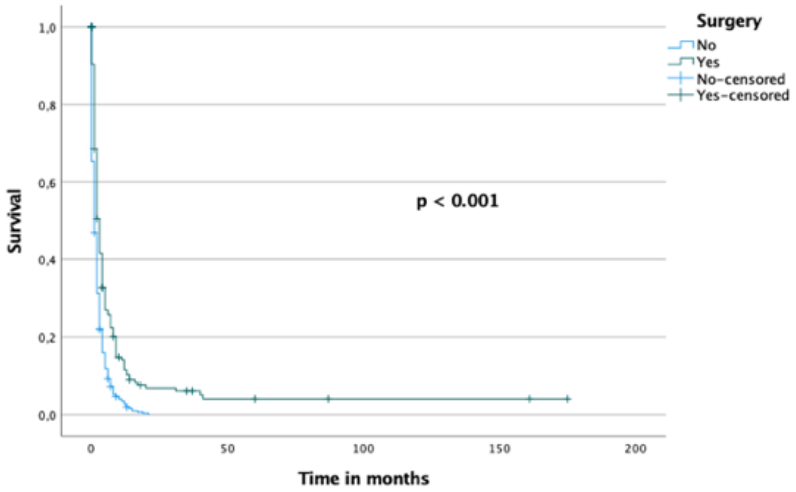
[137] N. Onoda, I. Sugitani, K. Ito, A. Suzuki, T. Higashiyama, T. Fukumori, N. Suganuma, K. Masudo, H. Nakayama, A. Uno, K. Yane, S. Yoshimoto, A. Ebina, Y. Kawasaki, S. Maeda, M. Iwadate, und S. Suzuki, „Evaluation of the 8th Edition TNM Classification for Anaplastic Thyroid Carcinoma“, *Cancers*, Bd. 12, Nr. 3, S. 552, Feb. 2020, doi: 10.3390/cancers12030552

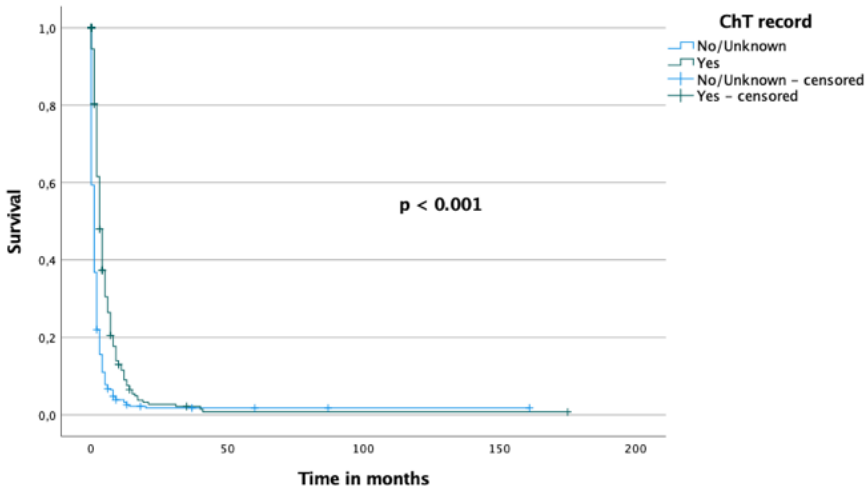
[138] I. Sugitani, Y. Hasegawa, M. Sugasawa, M. Tori, T. Higashiyama, M. Miyazaki, H. Hosoi, Y. Orita, und H. Kitano, „Super-radical surgery for anaplastic thyroid carcinoma: A large cohort study using the anaplastic thyroid carcinoma research consortium of Japan database: Super-radical surgery for anaplastic thyroid carcinoma“, *Head Neck*, Bd. 36, Nr. 3, S. 328–333, März 2014, doi: 10.1002/hed.23295

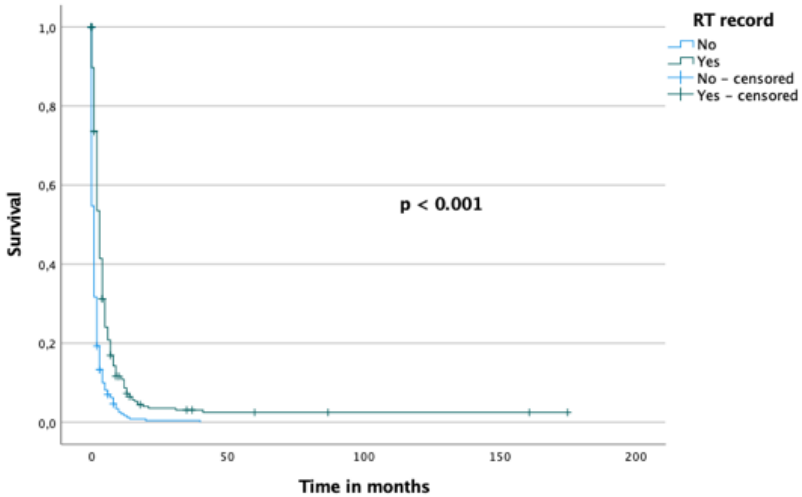
[139] M. Troch, O. Koperek, C. Scheuba, K. Dieckmann, M. Hoffmann, B. Niederle, und M. Raderer, „High Efficacy of Concomitant Treatment of Undifferentiated (Anaplastic) Thyroid Cancer with Radiation and Docetaxel“, *J. Clin. Endocrinol. Metab.*, Bd. 95, Nr. 9, S. E54–E57, Sep. 2010, doi: 10.1210/jc.2009-2827

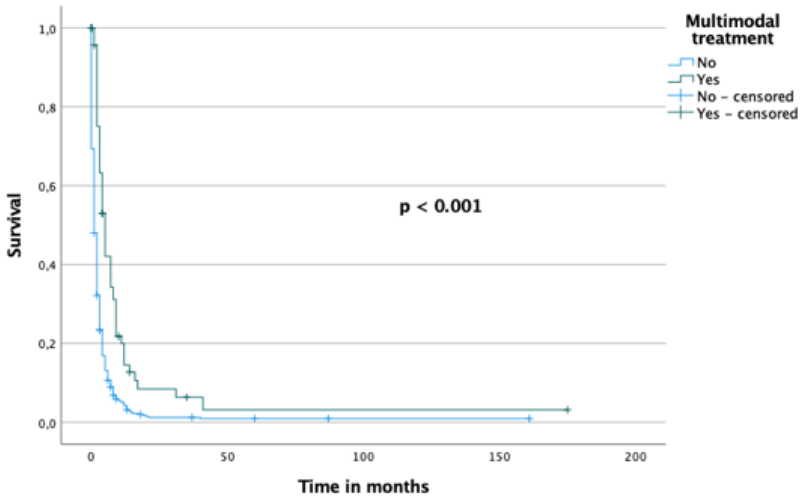
Anhang A: Supplementary Material zum Paper IV

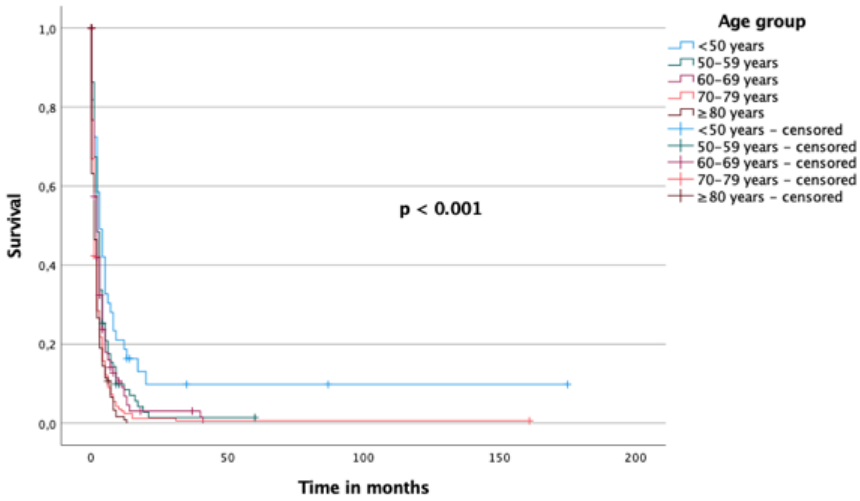
Figures 1A-F. Kaplan-Meier curves of prognostic factors for OS in the whole SEER cohort (n = 617)

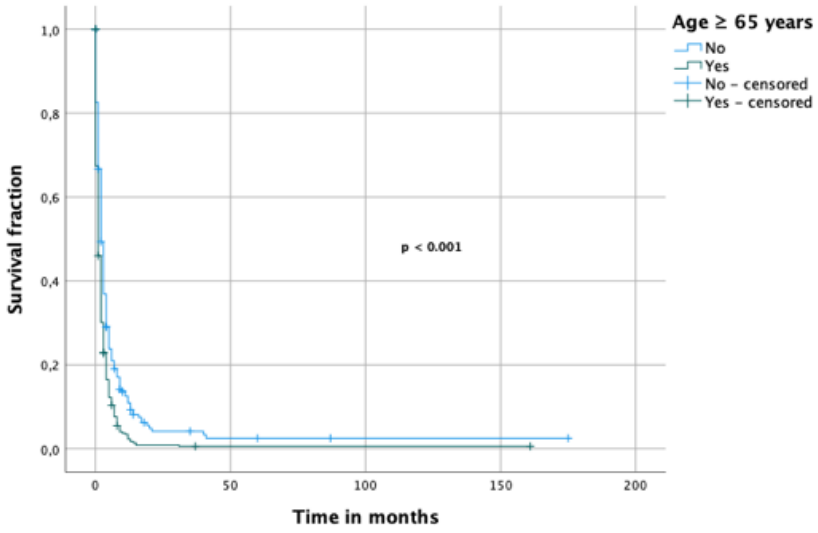




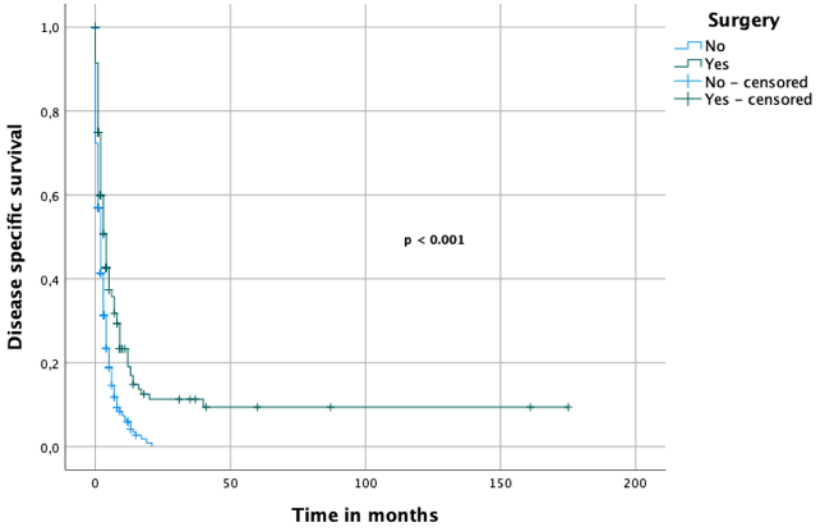


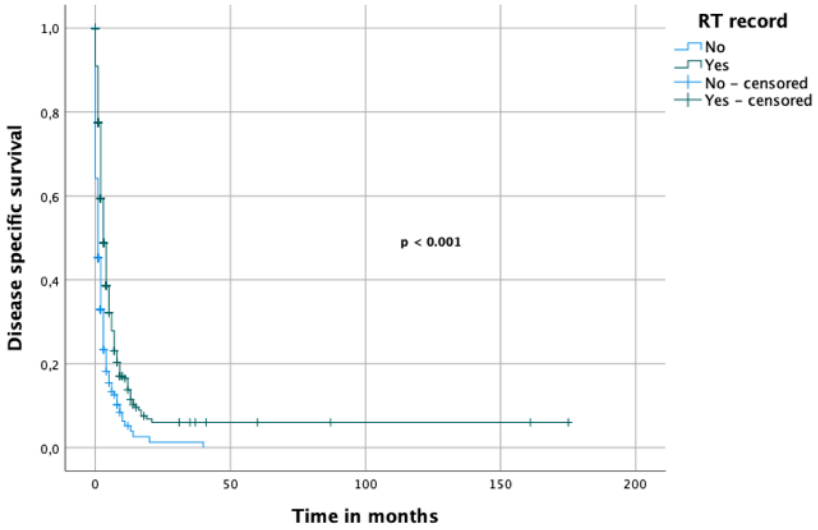

Multimodal treatment
No
Yes
No – censored
Yes – censored
Survival
1,0
0,8
0,6
0,4
0,2
0,0
p < 0.001
0
50
100
150
200
Time in months

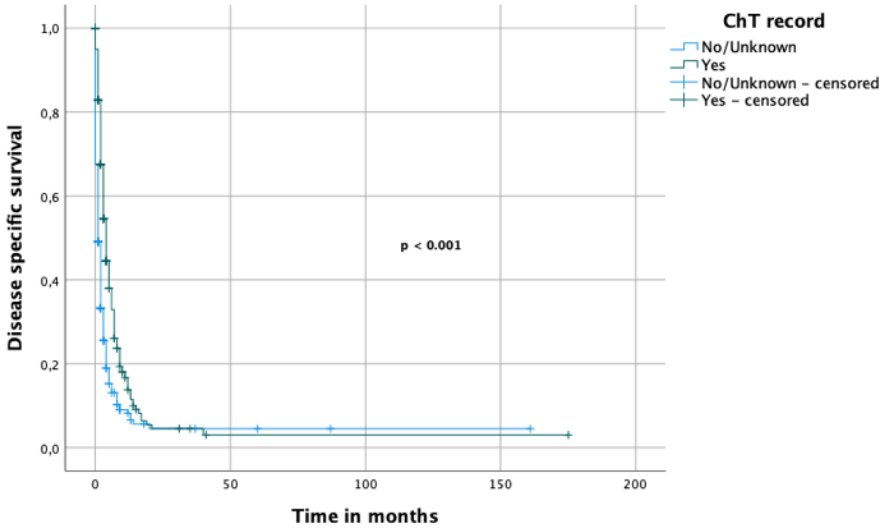

Age group
<50 years
50–59 years
60–69 years
70–79 years
≥80 years
<50 years – censored
50–59 years – censored
60–69 years – censored
70–79 years – censored
≥80 years – censored
Survival
1,0
0,8
0,6
0,4
0,2
0,0
p < 0.001
0
50
100
150
200
Time in months

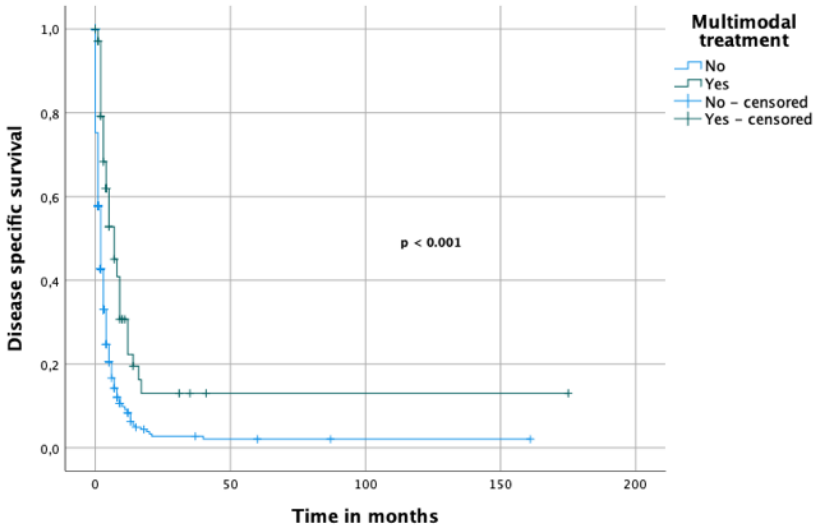

Age ≥ 65 years
No
Yes
No – censored
Yes – censored
Survival fraction
1,0
0,8
0,6
0,4
0,2
0,0
p < 0.001
0
50
100
150
200
Time in months

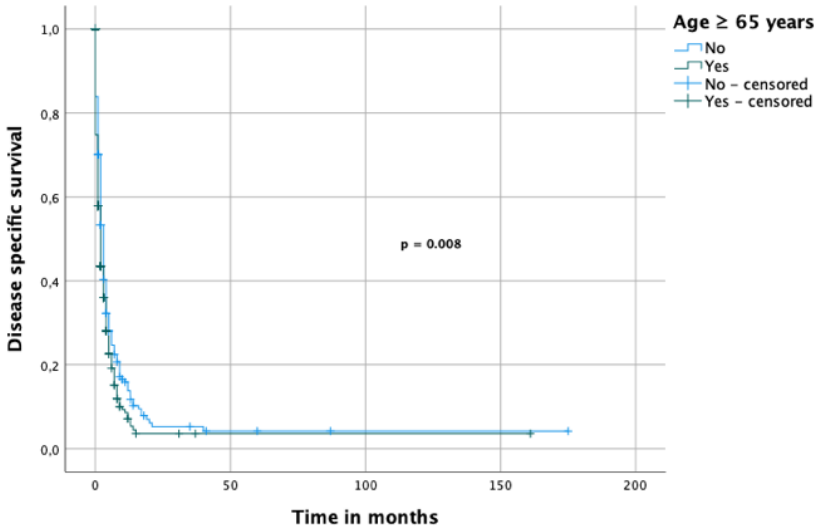
Figures 2A-F: Kaplan-Meier curves of prognostic factors for DSS in the whole SEER cohort (n = 617)

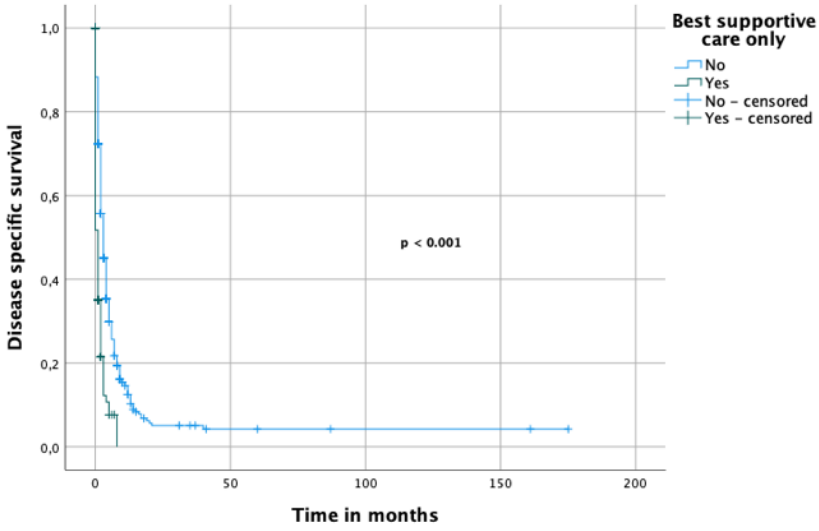




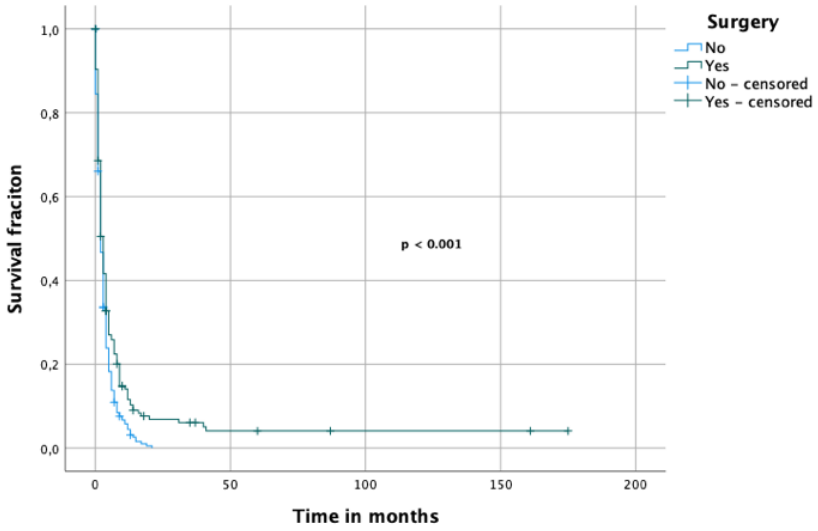


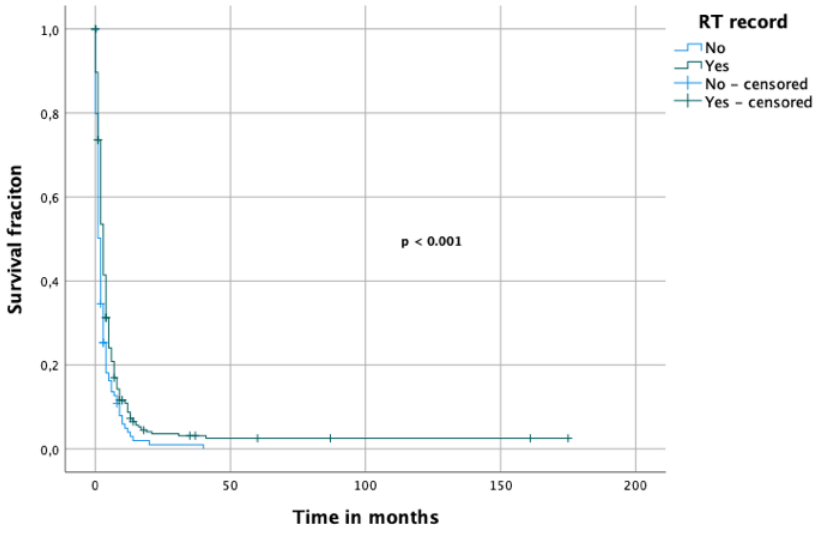

Multimodal treatment
No
Yes
No – censored
Yes – censored
Disease specific survival
1,0
0,8
0,6
0,4
0,2
0,0
p < 0.001
0
50
100
150
200
Time in months

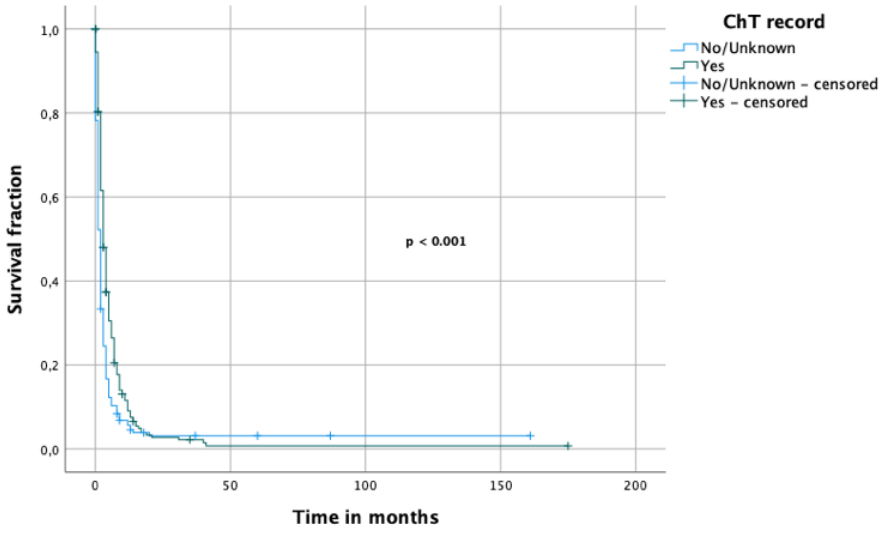

Age ≥ 65 years
No
Yes
No – censored
Yes – censored
Disease specific survival
1,0
0,8
0,6
0,4
0,2
0,0
p = 0.008
0
50
100
150
200
Time in months

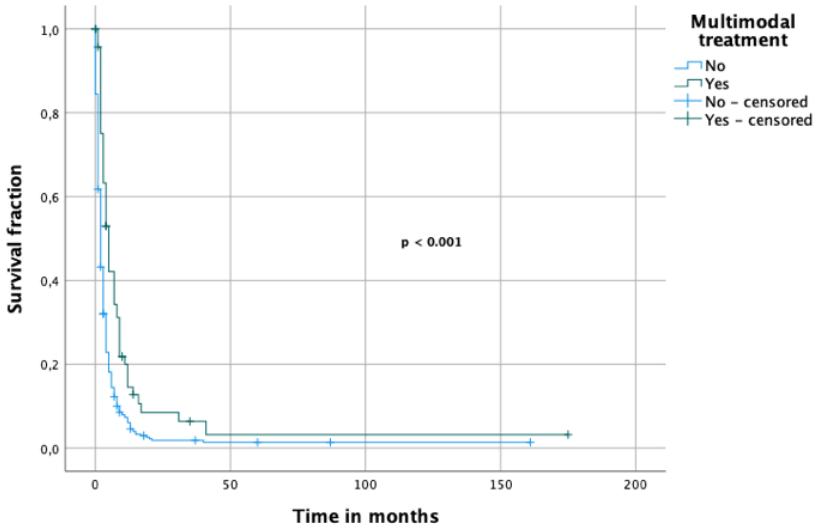

Best supportive care only
No
Yes
No – censored
Yes – censored
Disease specific survival
1,0
0,8
0,6
0,4
0,2
0,0
p < 0.001
0
50
100
150
200
Time in months

Figures 3A-E. OS of patients from the SEER cohort undergoing any tumor directed treatment.








Multimodal treatment
No
Yes
No – censored
Yes – censored
Survival fraction
1,0
0,8
0,6
0,4
0,2
0,0
p < 0.001
0
50
100
150
200
Time in months

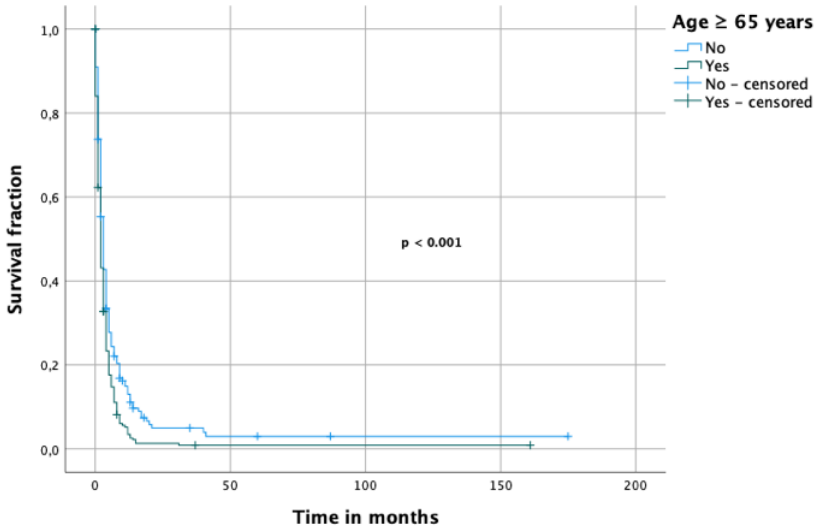
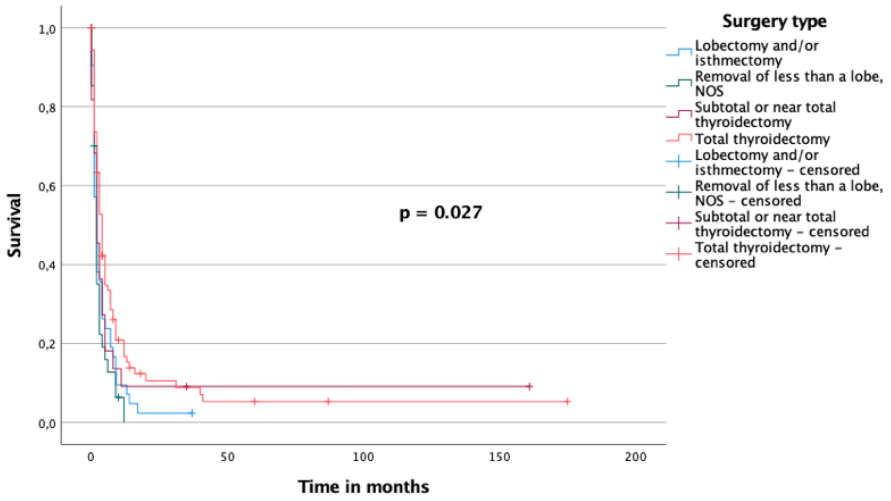
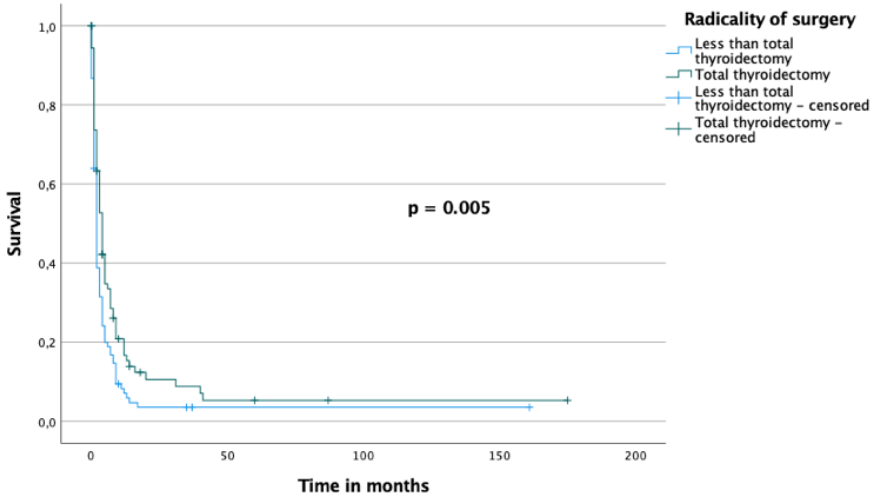
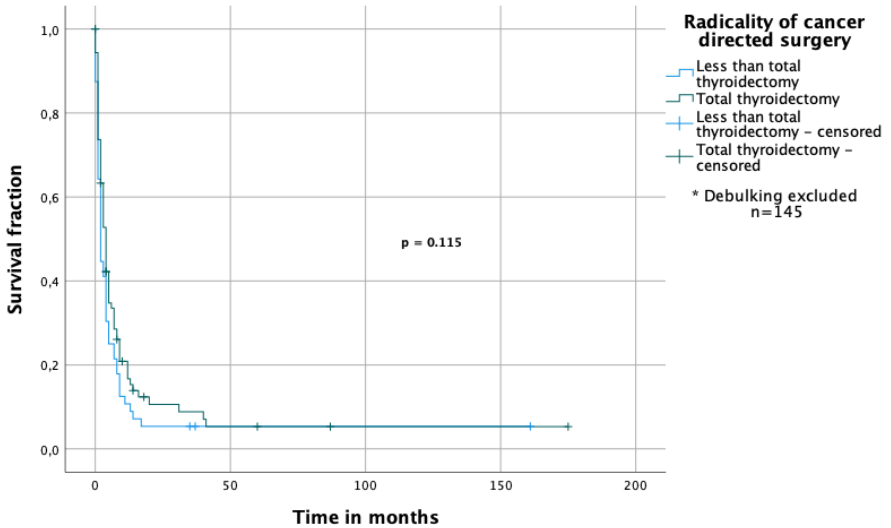
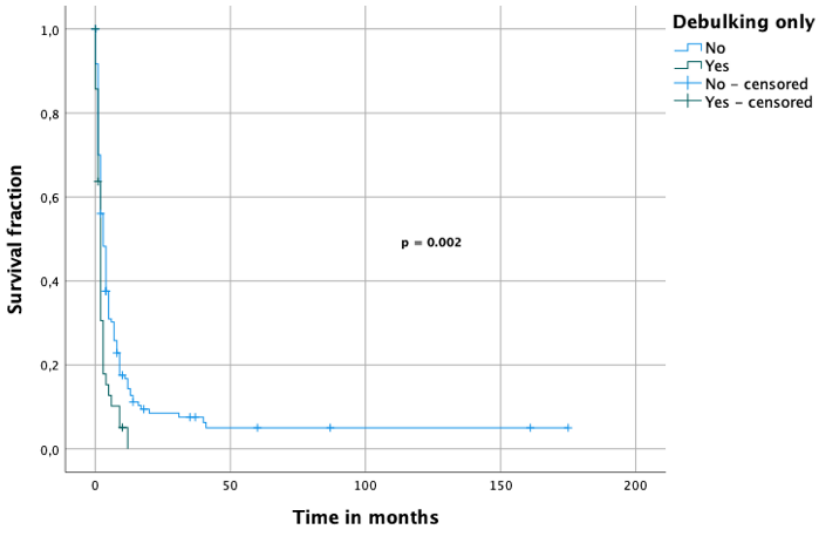

Age ≥ 65 years
No
Yes
No – censored
Yes – censored
Survival fraction
1,0
0,8
0,6
0,4
0,2
0,0
p < 0.001
0
50
100
150
200
Time in months

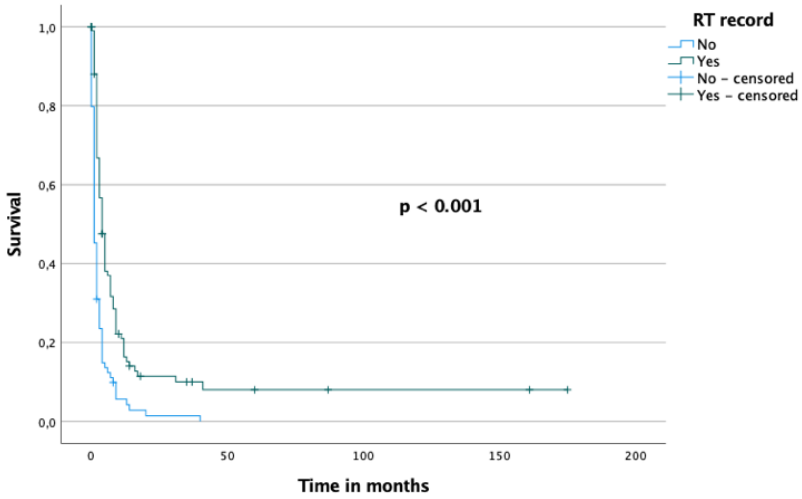
Figure 4A-I. OS of operated cohort from the SEER database

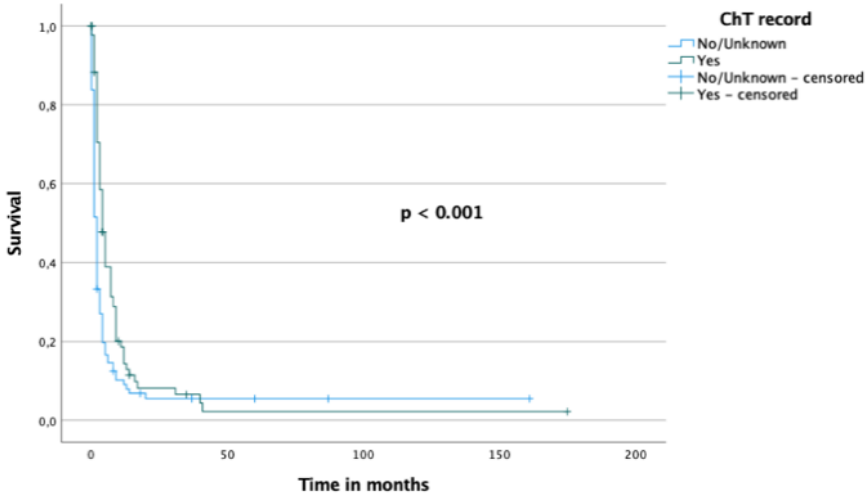


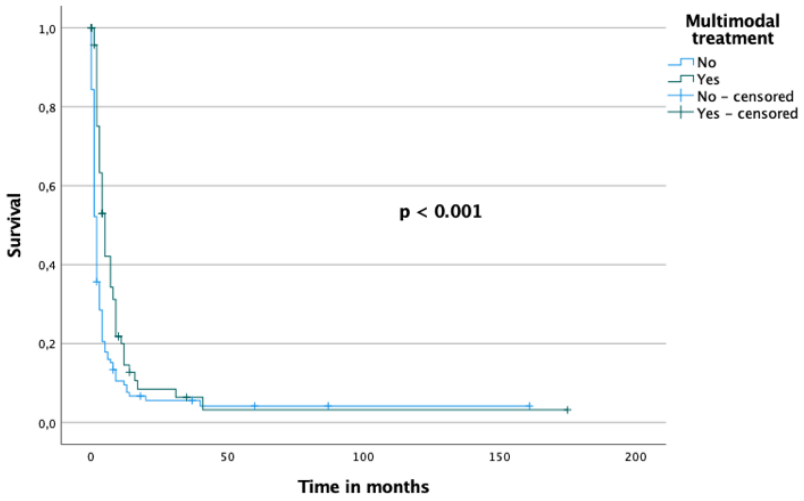


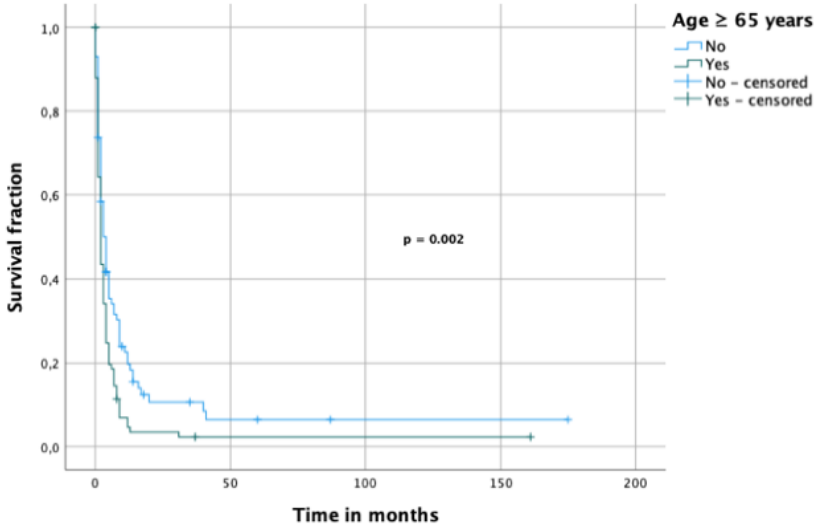



Debulking only
No
Yes
No – censored
Yes – censored
Survival fraction
1,0
0,8
0,6
0,4
0,2
0,0
p = 0.002
0
50
100
150
200
Time in months


RT record
No
Yes
No – censored
Yes – censored
Survival
1,0
0,8
0,6
0,4
0,2
0,0
p < 0.001
0
50
100
150
200
Time in months


ChT record
No/Unknown
Yes
No/Unknown – censored
Yes – censored
Survival
1,0
0,8
0,6
0,4
0,2
0,0
p < 0.001
0
50
100
150
200
Time in months


Multimodal treatment
No
Yes
No – censored
Yes – censored
Survival
1,0
0,8
0,6
0,4
0,2
0,0
p < 0.001
0
50
100
150
200
Time in months


Age ≥ 65 years
No
Yes
No – censored
Yes – censored
Survival fraction
1,0
0,8
0,6
0,4
0,2
0,0
p = 0.002
0
50
100
150
200
Time in months

Danksagung

An dieser Stelle möchte ich mich bei allen Personen bedanken, ohne deren aktive Mitwirkung meine Promotion und die Publikationen nicht möglich gewesen wären. Besondere Dankbarkeit richte ich an die Betreuer meiner Doktorarbeit, nämlich Herrn Prof. Claus Belka, Frau Prof. Christine Spitzweg und Herrn Prof. Maximilian Niyazi. Ich bedanke mich für Ihre großartige fachliche Unterstützung, die mir gegebenen Möglichkeiten und ein immer sehr angenehm gestaltetes Arbeitsklima.

Außerdem möchte ich bei Frau Dr. Josefine Rauch und Herrn Dr. Lukas Käsmann bedanken, die mich vom ersten bis zum letzten Tag der Promotion tatkräftig unterstützt haben. Es war ein großes Vergnügen mit Ihnen in einem Team der „ATC-Gruppe“ arbeiten zu dürfen! Auch gegenüber Frau Teresa Augustin, meiner Kollegin in der „ATC-Gruppe“, möchte ich ebenfalls meine Dankbarkeit für die großartige Mitarbeit, Aufmunterungen und die wertvollen Beiträge zu den Publikationen ausdrücken.

Schließlich bedanke ich mich bei meiner lieben Familie, und zwar allen voran bei meinen Eltern: Herrn Prof. Ihor Oliinyk und Frau Dr. Liudmyla Oliinyk. Ich danke euch für eure Unterstützung, eure Ratschläge und eure Weisheit. Ich bedanke mich ebenfalls bei meinem Onkel Herrn Volodymyr Fedonchuk und meiner Tante Frau Elvira Romashchenko. Ohne euren Glauben an mich, hätte ich vermutlich nie ein Medizinstudium in München beginnen können! Meiner Schwester Iryna gilt ein besonderer Dank für die zahlreichen stundenlangen Telefonate, die netten Worte und ihre Unterstützung.

Darüber hinaus bedanke ich mich bei meinen besten Freunden: Vlad, Kostya, Yurii und Eugen. Ihr wart immer für mich da!

Lebenslauf