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Klinikum der Ludwig-Maximilians-Universität München

Dosimetric analysis of radiotherapy in prostate cancer patients with pelvic or paraaortic lymph nodes involvement

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1. Introduction

1.1 Epidemiology of prostate cancer

Prostate cancer is the most common malignancy diagnosed in urological system of men worldwide.[1] The incidence of prostate cancer has been significantly increasing in the recent years, and it causes approximately 25,6000 deaths per year.[2,3] The high morbidity of prostate cancer is mainly attributed to the improving diagnostic techniques which include transrectal ultrasound (TRUS),[4] biopsy,[5] in particular to the determination of the PSA value.[6] It has been widely acknowledged that prostate cancer consists of indolent and aggressive varieties.[7] Among these diagnosed cases, approximately ninety percent are localized cancer, and the rest are diagnosed as advanced or metastatic disease. Most localized prostate cancer are indolent and do not progress to aggressive disease during a patient's lifetime. Generally speaking, patients with localized prostate cancer exhibit an overall low mortality,[8] while those with advanced or metastatic prostate cancer have a much worse prognosis.[9,10] In addition, even for the patients with a same disease stage, the clinical outcomes vary dramatically due to individual and genomic differences.[11]

1.2 Risk factors of prostate cancer

As many other tumor diseases, the etiology of prostate cancer remains largely unclear despite intensive research efforts. However, epidemiological data from cancer registries show that one of the most important risk factor of the development of this

malignancy is age. The number of new cases peaks in the 70-74 age group, while the incidence approaches zero before the age of 35. A positive family history has now also been identified as an independent risk factor by means of meta-analysis. There was a relative risk for any first-degree relative of around 2.5, which, however, can increase a lot if several family members are affected or if the relative is younger. This suggests a hereditary form of prostate cancer, which is determined according to the following criteria: Prostate cancer must be diagnosed in a family in at least three first-degree relatives, three generations in a row, or in two brothers with an age of onset <55 years old.[12] Many studies attempted to search for susceptibility genes, i.e. those that increase the risk of the disease, have produced numerous genetic variants and mutations in a wide variety of genes that are associated with the disease.[13] However, the data available so far cannot correctly identify a trigger gene, and this fact suggests a pronounced heterogeneity and complexity of genetic inheritance. Asians are generally less likely to develop the tumor, which has been attributed to the traditional, low-fat, high-calorie diet.[14] The assumption of genetic ethnic differences is also reasonable, although it has been shown that, for example, Asians who emigrate to the USA as adolescents match the incidence rate of the general US population.[15]

1.3 Clinical features of prostate cancer

Prostate cancer can hardly cause illustrious symptoms at its early stage. As the majority of malignancies grow very slowly and are localized in the peripheral zone, and

therefore are not illustrious through pain or symptomatic narrowing of the urethra. However, obstructive micturition disorders such as pollakiuria, nocturia or dysuria in advanced prostate cancer are often the first clinical signs.[16] In addition, hematuria, erectile dysfunction or continence disorders can occur.[16] If metastasis has already occurred, bone pain or even pathological fractures, lymphedema with pronounced lymphogenic metastasis, pronounced B symptoms or cerebral tumor settlements are rare complications and should be viewed as late symptoms of a metastatic disease.[17]

1.4 Pathological features of Prostate Cancer

Based on the McNeal Zonal Classification of prostate gland, the majority of prostate cancers (70-75%) are found in the peripheral zone, as this is where the vast majority of prostatic glandular tissue is located. These are often clinically manifest carcinomas, while the remaining 25-30% in the central (10%) or the transitional zone (15-20%) are more incidental.[18]

According to their clinical appearance and the associated symptoms, they are further described as several stages: From the point of origin, prostate cancer usually grows in the direction of the apex within the organ or infiltrates the neighboring zones. If the capsule of the prostate has already been breached, one speaks of a locally advanced carcinoma, which mainly spreads through the perineural clefts of the nerve passage points. With further lymphogenic progression of the disease, after infiltration of the prostate's own drainage system, the malignancy first affects the periprostatic-

lymphatic network and then spreads to the regional, i.e. still pelvic lymph nodes. When the cancer cells spread to the bifurcation of the common iliac artery, it means a regional lymph node metastasis. After the first lymph node stations of the obturator fossa and the iliac vessels, the carcinoma can spread further into the sacral or inguinal lymph node stations to the paraaortic, mediastinal or even supraclavicular nodules.

The prostate carcinoma hematogenous spread into the skeletal system, where it tends to form bone metastases, which can be detected in 85% of patients who have died of prostate carcinoma. The trunk skeleton with lumbar vertebrae, the pelvis, thoracic vertebrae, the ribs, the sternum, the proximal part of the femora, but also the cervical vertebrae and the skull and humeri are affected most frequently. Metastases in the area of visceral organs, such as the lungs, the adrenal glands or the liver, are less common. In most cases, a lymphogenic spread occurs first, and later hematogenous metastasis takes place.

1.5 TNM Classification

Prostate cancer is categorized to different stages by the Union International Cancer Control (UICC) with the TNM classification: the status of the primary tumor site and size (T), the regional lymph node status (N) and the presence of metastases (M), WHO grading (G) and the status of the resection margin (R).[19]

The T describes the extent and the behavior of the primary tumor and is divided into four subgroups: T1 means a clinically inapparent tumor that is not palpable and cannot

be detected by imaging techniques. T2 stands for all tumors that are limited to the prostate. T3 are tumors that cross the prostate capsule. T4: The tumor is fixed, or it is growing into nearby structures other than the seminal vesicles[20] (Figure 1).

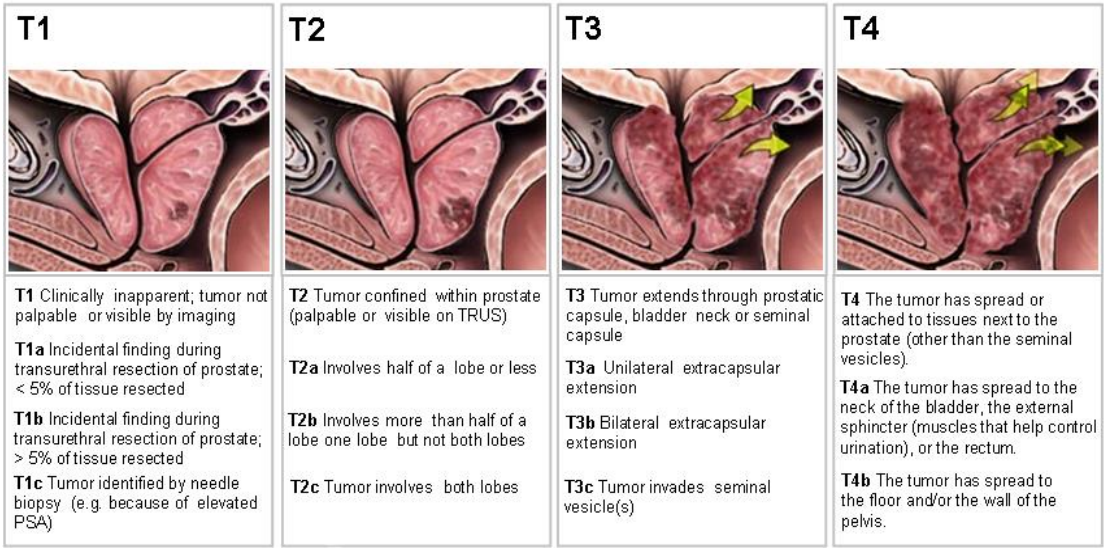

Figure 1. T stage describes the primary tumor size and location of the tumor (from Chris Foster, Prostate Matters).

The small p - i.e. pT1, pT2, pT3, pT4 - means “pathological” and indicates that the tumor stage was determined in the resected histological specimen. In contrast, a small c - i.e. cT1, cT2, cT3, cT4 - indicates a tumor stage clinically recognized by digital rectal examination (DRE).[21]

The absence or presence of regional lymph node metastases is categorized to N0 and N1. N0 means that there are no regional lymph node metastases, and N1 describes the presence of regional lymph node metastases.[20]

The presence of distant metastases, that is, the hematogenous spread of the primary tumor is described by M. M0 means no distant metastases, M1 means that distant

metastases are present and Mx describes the presence of distant metastases cannot be assessed.[20]

Another classification of the malignancy of prostate cancer is the differentiation grades of the WHO. The differentiation grades are described as well differentiated (G1), moderately differentiated (G2) and poorly differentiated or undifferentiated (G3), taking into account both structural and cytological aspects.

The tumor margins of the prostatectomy specimen are categorized to R0, R1, and R2. R0 means resection for cure or complete remission. R1 means microscopic residual tumor, and R2 means macroscopic residual tumor.[22]

1.6 Histological grading

The Gleason score (GS) was firstly proposed in 1966 when it was described by the American pathologist Donald Gleason for the histological classification of prostate cancer. It assesses the differentiation of different cell populations on a scale from 1 (tissue best differentiated) to 5 (undifferentiated), whereby the sum of the two predominant types of cell differentiation after radical prostatectomy defines the final value. In a punch biopsy of the prostate, the calculation is based on the most common Gleason score and the least differentiated tissue[23] (as shown in Figure 2).

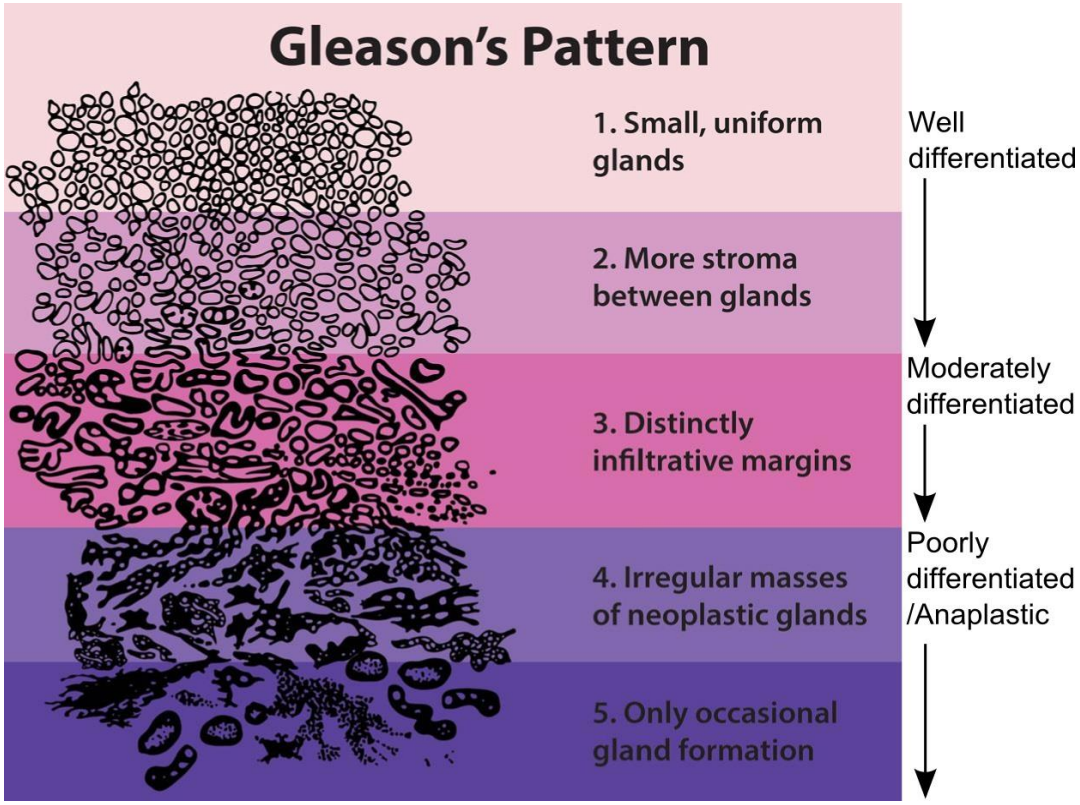

Figure 2. Gleason score classification according to the degree of differentiation of the prostate carcinoma cells (from Wikimedia Commons, 2019).

The Gleason score correlates with the PSA value, the TNM classification, the volume of the tumor, the lymph node status, the recurrence and survival rate and other prognostic factors.[24]

1.7 Treatment options for prostate cancer

Radical prostatectomy (RPE) and primary radiotherapy (RT) form the backbone of the local treatment of prostate cancer with curative intent. Due to the parallel survival benefits and different spectrum of side effects caused by the two treatment options, neither RPE alone nor RT alone was adopted as a standard therapy by the German

(DGU), the European (EAU) and the American (AUA) guideline. In addition, in many cases the final therapy decision also depends on the patient's personal preferences.[18,25,26]

1.7.1 Active surveillance (AS)

Due to the improved diagnostic methods and a growing awareness of prostate cancer management, tumors can be more often detected at an early stage (e.g. T1 prostate cancer). As an alternative to immediate invasive therapy, low-risk patients can be closely monitored so that therapeutic intervention should be adopted if the cancer has progressed. For many males, this can not only mean postponing invasive therapy, but can also prevent overtreatment.[27] According to the current German S3 guideline, the following parameters shown in Table 1 are decisive for prostate cancer that does not require necessary treatment. A further tumor control must be carried out every three months after the initial diagnosis in the first two years by means of a PSA value determination and a DRE. If the results remain stable, six-monthly checks can then be arranged.[18]

Risk parameters	Inclusion criteria
PSA	⩽ 10 ng/ml
Gleason Score	⩽ GS 6
Clinical tumor stage	T1 – T2a
Punch biopsy	Tumor in ≤ 2 punches with removal of 10-12
Single punch	≤ 50% tumor per punch

Table 1. Inclusion criteria for active surveillance according to the German S3 guideline.

1.7.2 Radical prostatectomy and pelvic lymphadenectomy

Radical prostatectomy (RPE) is still the only procedure that has shown an improvement in tumor-specific and metastasis-free survival in a randomized study compared to a conservative “watchful waiting” strategy.[28] Based on the original perineal surgical technique, the current surgical methods become more advanced and mature. For example, modern nerve-sparing and minimally invasive surgical procedures such as retropubic (RRP), laparoscopic (LRP), and robot-assisted radical prostatectomies (RARP) are available. From the tumor-surgical point of view, all procedures can now be regarded as approximately equivalent, and regional lymphadenectomy (LAE) can also be performed with any method. The most common side effects of radical prostatectomy are urinary incontinence and possible impotence. With the further development of surgical techniques, local tumor control can be improved and postoperative complications can be reduced.

1.7.3 Watchful waiting (WW) and Androgen deprivation therapy (ADT)

“Watchful waiting” (WW), as well as primary androgen deprivation, are two treatment methods that are used in a palliative setting. Similar to "Active Surveillance", in the context of "Watchful Waiting", no interventional therapy will be considered as long as no complications arise from tumor progression. However, with regard to the patient groups to whom these treatment strategies can be offered, the two procedures differ a lot from each other. In patients under 65 years old with a life expectancy of over 10 years, WW is inferior to radical prostatectomy. As these patients should be treated curatively and an "active surveillance" strategy is only possible if the inclusion criteria mentioned above are met.[18,28] In contrast, patients who do not meet these criteria, who have a low life expectancy (<10 years) or who have severe comorbidities can be included in the WW. In this case, the goal of treatment is not healing, but maintaining the quality of life.[29]

Androgen deprivation therapy (ADT) is the first-line treatment for advanced or metastatic prostate cancer.[30] ADT is recommended before, during or after definitive radiotherapy for intermediate and high-risk localized prostate cancer. Androgen deprivation in prostate cancer makes use of the testosterone-dependent growth of both the prostate and prostate cancer by producing a drug-induced testosterone deficiency (Figure 3).

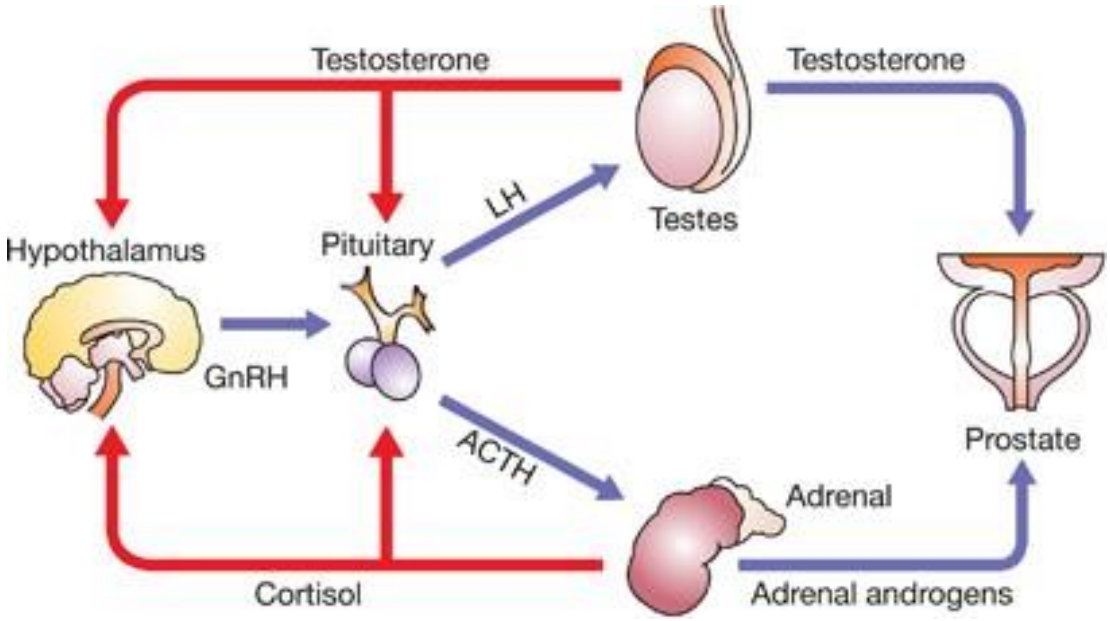

Figure 3. Endocrine control of the prostate gland (from N D Shore et al. 2013, Prostate Cancer and Prostatic Diseases).

The testicular androgen release is regulated by the pituitary gland, namely by the luteinizing hormone (LH) and its releasing hormone gonadotrophin-releasing hormone (GnRH). The administration of a GnRH agonist counteracts the physiological, pulsatile release and leads permanently to the exhaustion of the LH release and thus to the cessation of testosterone production. The serum testosterone level drops to the castration level. GnRH agonists, which practically cause a pharmacological hypophysectomy, can be administered as a 4-week depot injection or as a 3-month depot injection.

1.7.4 Primary radiation therapy

Based on the escalation of the radiotherapy dose that has taken place in the last two decades and the favorable treatment outcomes of primary radiotherapy, its validity is

becoming equivalent with radical prostatectomy. Initially, the technique was three-dimensional (3D) conformal radiotherapy, which has now been replaced by Intensity-modulated radiation therapy (IMRT) and modulated rotary radiation therapy (Volumetric Modulated Arc Therapy - VMAT). The representative images of VMAT strategy in three different dimensions were shown in Figure 4 (from Klinik und Poliklinik für Strahlentherapie und Radioonkologie, LMU Klinikum).

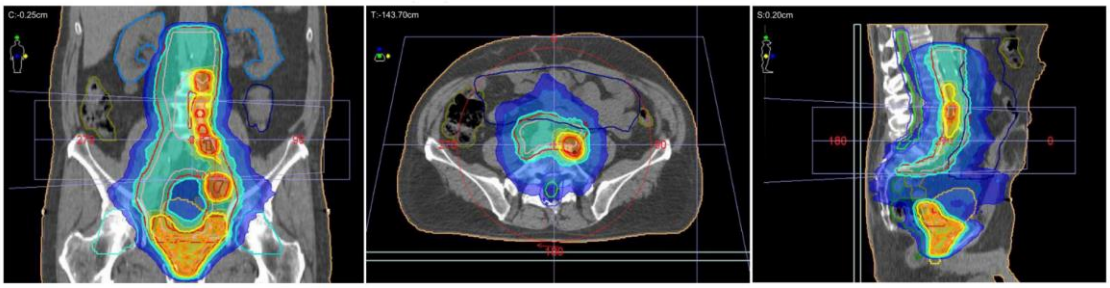

Figure 4: Representative images of VMAT strategy in three different dimensions (from Klinik und Poliklinik für Strahlentherapie und Radioonkologie, LMU Klinikum).

The dose is put together using small, irregular fields, namely segments, as in a mosaic from different angles of incidence. A radiation-absorbing diaphragm system that can be precisely positioned, the so-called multileaf collimator in the head of the irradiation device, allows each individual segment to be specifically aligned for the respective irradiation volume in each patient. With IMRT, the radiation device is positioned around the patient at fixed angles. With the VMAT irradiation technique, on the other hand, the irradiation device rotates continuously around the patient one or more times. IMRT and

VMAT radiation technology require that strongly irregularly shaped radiation volumes can be well covered while at the same time optimally protecting the organs at risk.

A meta-analysis of a total of 23 individual studies showed that the IMRT technique, compared to three-dimensional conformal radiotherapy, is associated with a significantly lower rate of acute and long-term gastrointestinal side effects and late complications such as hematochezia while at the same time providing better biochemical control.[31] Because of this, the German S3 guideline also recommends performing definitive radiotherapy using the IMRT technique using image-guided techniques, the so-called IGRT technique (Image-guided radiation therapy).[18]

The IGRT technique is the use of imaging methods during radiation therapy, on the one hand to increase the precision and accuracy of the radiotherapy and, on the other hand, to control the position of the surrounding organs at risk, such as the bladder and rectum, during definitive radiotherapy of the prostate. In principle, a distinction is made between interfractional movements of the prostate and organs at risk, i.e. differences in position that arise between the individual sessions, and intrafractional movements, i.e. movements of the target volume or organs at risk during radiation. Intrafractional movements are in particular due to the mobility of the organs during breathing. Depending on the various filling states of the rectum and bladder, the prostate can move by more than 1cm.[32] Typical IGRT imaging procedures before and during radiotherapy are ultrasound, MRI, x-rays of the bony structures, computed tomography (CT) and surface scanners. For better orientation, gold markers can also be placed transrectally in the prostate in patients prior to definitive radiotherapy of the prostate.

1.7.4.1 Post - operative radiotherapy

Additional radiation after surgery can improve progression-free survival in locally advanced tumors and should therefore be offered to patients at risk.[33] If the postoperative PSA value is lower than the detection limit, adjuvant radiotherapy (ART) will be performed within 10-12 weeks after surgery. While A salvage radiation (SRT) will be carried out when the PSA value is not falling or rising again. In normal fractionation (ED 1.8-2.0 Gy), total doses of 64 to a maximum of 70 Gy are recommended in the case of postoperative PSA increase or in the adjuvant therapy situation. As a result, despite the presence of locally advanced prostate cancer, higher local tumor control can be observed in 95% of patients with an R1 resection. According to the recommendations of the German S3 guideline, patients with capsular infiltration, corresponding to stage pT3, should be offered adjuvant radiotherapy, regardless of the incision margins. In addition, this strategy can be also offered to patients with a smaller local tumor size (≤ pT2) but a positive incision margin. The radiation itself lasts 6 - 7 weeks due to the dose fractionation and is usually carried out on an outpatient basis. If adjuvant radiotherapy is generally given to these high-risk patients to obtain proven biochemical recurrence-free survival benefits, then about half of the patient population may be over-treated without affecting survival. Therefore, the question of the optimal patient selection is difficult.

1.7.4.2 Adverse events (AE) of radiotherapy

The adverse events of radiotherapy vary from person to person, and are related to the patients' overall health and the type, location, and dose of radiotherapy they received.[34] Common side effects of radiotherapy for prostate cancer include burning sensation when urinating, pollakiuria, and anal inflammation.[35] This is because the organs around the prostate, especially the bladder and rectum, are also slightly exposed. These symptoms usually appear midway through the course of treatment and disappear within a few months after the course of treatment. In addition, patients may also experience lower urinary tract symptoms (LUTS) or erectile dysfunction. We evaluate the side effects according to Common Terminology Criteria for Adverse Events v4.03 (CTCAE), which was published by U.S. Department of Health and Human Services on June 14, 2010. The CTCAE displays Grades 1 through 5 with unique clinical descriptions of severity for each AE based on this general guideline (Table 2):

Table 2. Clinical descriptions of severity for each AE Grade(CTCAE).

Grade 1	Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.
Grade 2	Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental ADL.
Grade 3	Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care ADL.
Grade 4	Life-threatening consequences; urgent intervention indicated.
Grade 5	Death related to AE.

2. Materials and methods

2.1 Patient enrollment and data collection

We retrospected the hospitalization records of all prostate cancer patients in the recent ten years (from 2011 to 2021) in the Department of Radiation Oncology, LMU hospital. The enrollment criterion of study subjects is as follows: at least one positive lymph node (LN) is observed at the lymphatic drainage area of prostate before radiation therapy, including paraaortic LN, common iliac LN, internal iliac LN, external iliac LN, sacral LN, and inguinal LN (As shown in Figure 5).

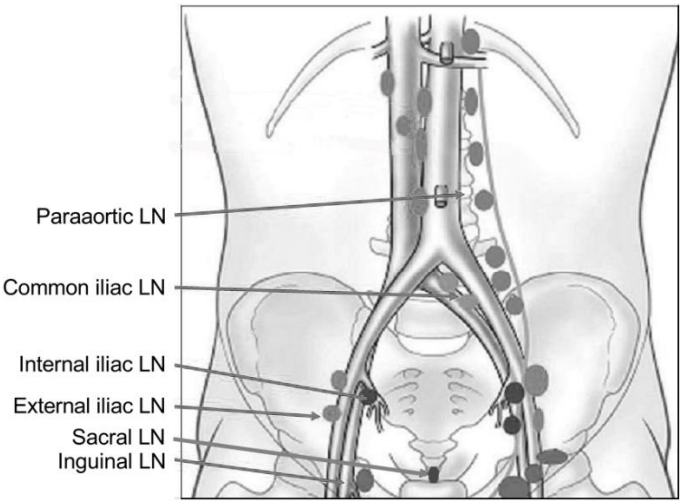

Figure 5: Enrollment criterion: at least one positive lymph node was observed at the lymphatic drainage area of prostate before RT.

Finally, a total of 126 eligible prostate cancer patients with above-mentioned positive lymph nodes before radiation therapy were included in our study, and their full-scale clinicopathological features were recorded, including clinical or pathological TNM staging data, Gleason score, radiotherapy approaches, with or without ADT, PSA

values (at different stages), lymph node EQD, LN recurrence (outfield or infield) after RT, biochemical recurrence survival information etc. The Gleason score of each prostate cancer sample was classified to six levels: 6, 7a, 7b, 8, 9, 10. LN recurrence in radiation field before June 1st 2021 was defined as “infield LN recurrence”, and LN recurrence out of radiation field before June 1st 2021 was defined as “outfield LN recurrence”. Density diagrams of LN EQD2/3 and EQD2/1.5 that prostate cancer patients received were plotted to illustrate their density, relationship, and distribution difference, and the peak of density diagram represents the highest population. Proportion pie charts were plotted to depict the ratio of patients who received RT or ADT among all the enrolled 126 patients.

2.2 Survival analyses

For survival analysis, 115 patients with full-scale biochemical recurrence survival information (BCR event and follow-up time) were included. To investigate the survival impact of different parameters, the 115 patients were divided into several groups labelled with different parameters respectively: different radiotherapy approaches (VMAT or IMRT), whether received ADT during RT (RT with ADT, RT without ADT), different LN EQD2/3 dose (< median or > median). The Kaplan-Meier method was used to draw survival curves, and the log-rank test was performed to evaluate survival difference between two groups. For the total of 115 patients, only one survival curve

was plotted to display their overall BCR-free survival. $P < 0.05$ was considered statistically significant.

2.3 PSA collection and normalization

PSA values at three different time points were collected, that is initial PSA value when diagnosed, PSA value before radiotherapy, and PSA nadir after radiotherapy. Considering PSA values are subject to geometric distribution and hard to compare using routine statistical methods, we normalized each recorded PSA value with $\log_{10}(x+1)$ transformed. By this way, the transformed PSA values were subject to approximate normal distribution, and routine statistical method such as group t-test could be applied to analyse the difference.

2.4 Difference analyses

Group t-test or one-way analysis of variance (ANOVA) was used to analyse the differences of transformed PSA value, Gleason score, LN EQD etc. among three groups: no recurrence group, only outfield LN recurrence group, and only infield LN recurrence group. $P < 0.05$ was considered statistically significant.

2.5 Correlation between ADT and LN recurrence

To investigate the relationship between ADT and LN recurrence, outfield or infield LN recurrence patients (n = 22) and patients without recurrence (n = 63) were further extracted for further study. Considering the data distribution is subject to 2 × 2 contingency table, chi-square test was suitable to analyze the correlation between ADT and LN recurrence. $P < 0.05$ was considered statistically significant.

3. Results

3.1 Data overview

Among all the 126 retrospective prostate cancer patients, 10 patients were categorized with clinical TNM stage, and the other 116 patients were categorized with pathological TNM stage. The detailed distribution is summarized in Table 3. We observed that the majority of these enrolled patients were diagnosed with pathological TNM stage because most of them (116/126) received radical prostatectomy, and their TNM stage was defined with pathological parameters of resection samples.

		Clinical	Pathological
T Stage	T1a	0	1(0.8%)
	T1b	1(0.8%)	1(0.8%)
	T1c	3(2.4%)	1(0.8%)
	T2a	0	1(0.8%)
	T2b	0	0
	T2c	0	19(15.1%)
	T3	4(3.2%)	0
	T3a	2(1.6%)	24(19.0%)
	T3b	0	65(51.6%)
	T4	0	4(3.2%)
N Stage	N0	2(1.6%)	61（48.4%）
	N1	8（6.3%）	53（42.1%）
	Nx	0	2(1.6%)
M Stage	M0	6（4.8%）	89(70.6%)
	M1	4(3.2%)	16(12.7%)
	Mx	0	11(8.7%)

Table 3: Summarization of clinical and pathological TNM staging information of the 126 enrolled prostate cancer patients in our study.

Furthermore, a detailed summarization of main clinical information of the 126 enrolled prostate cancer patients was shown in Table 4. These parameters include radiotherapy approaches (IMRT or VMAT), age when diagnosed, initial PSA, Gleason score, D'Amico Risk classification, radical prostatectomy or not, R status, lymphadenectomy (LAE), and positive lymph node numbers in lymphadenectomy (LAE LN+) etc.

		IMRT	VMAT	Total
Patient number (n)		27	99	126
Age diagnosed (44-84)	<60	7	12	19
	⩾60	20	87	107
Initial PSA(ng/mL)	Unknown	1	4	5
	<10	7	29	36
	10~20	6	27	33
	>20	13	39	52
Gleason Score	5~6	2	2	4
	7a	2	11	13
	7b	3	20	23
	8	6	16	22
	9	12	46	58
	10	2	4	6
D'Amico Risk Classification	Low	0	0	0
	Intemediate	1	1	2
	High	26	98	124
Radical Prostatectomy	Yes	24	92	116
	No	3	7	10
R Status	R0	9	44	53
	R1	14	42	56
	R2	0	1	1
	Rx	1	5	6
LAE	Yes	23	87	110
	No	1	5	6
LAE LN(+)	0	11	46	57
	1	1	17	18
	2	4	12	16
	3	2	4	6
	>3	5	6	11
	Unknown	0	2	2

Table 4: A detailed summarization of main clinical records of the 126 enrolled prostate cancer patients.

As regards to the treatment approaches for the 126 enrolled patients in our department, two main types of radiotherapy were applied. VMAT was applied to 76.38% of the entire patient cohort, while IMRT occupied the rest 23.62%. During radiotherapy, 78.91% patients received ADT, while the rest patients (21.09%) did not receive ADT. The proportion pie charts (Figure 6) illustrate the distribution of RT approaches and ADT among all the patients.

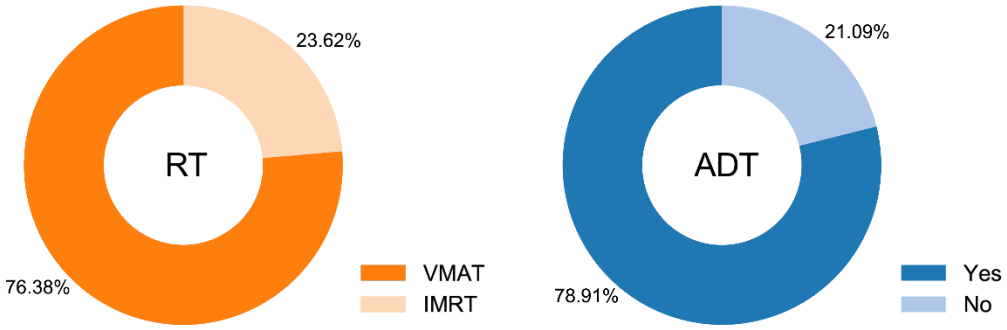

Figure 6: The proportion pie charts illustrate the distribution of RT approaches and ADT among all the 126 patients.

The LN EQD2/3 and EQD2/1.5 for each patient were extracted and compared, and density diagram was plotted to visualize the dose distribution for the global cohort. We observed that LN EQD2/3 and EQD2/1.5 exhibited a high consistency in the total 126 patients. The most frequently applied dose of LN EQD 2/3 is around 64 Gy, while 65 Gy for LN EQD2/1.5, and peaks were observed at corresponding position in the density diagram (Figure 7).

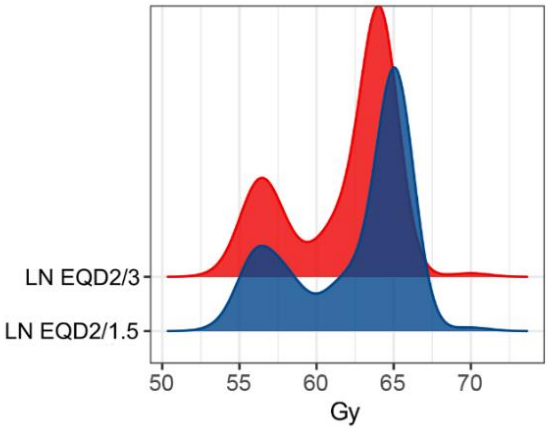

Figure 7: Population density diagram of LN EQD2/3 and EQD 2/1.5 of the 126 patients, and peaks represent the highest population for different doses.

3.2 Overall BCR-free survival analysis

After excluding patients without sufficient BCR or follow-up information, 115 patients remained with their BCR event (or not) and the follow-up time. The Kaplan-Meier method was used to plot the overall BCR-free survival curve for the 115 patients, and the result was shown in Figure 8. We observed that the BCR-free survival probability of 3-year is around 60%, 6-year less than 50%, and 9-year less than 40%. In general, this result indicated that although LN-positive prostate cancer patients received comprehensive treatments, the BCR-free survival is still unfavorable. On the other hand, there is an urgent need to investigate the relationship between different clinicopathological features such as positive lymph nodes in lymphatic drainage area of prostate and LN recurrence and prognosis.

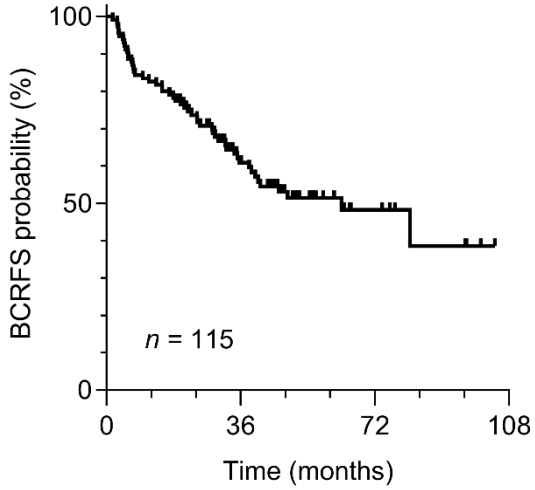

Figure 8: Overall BCR-free survival of 115 prostate cancer patients after RT. The BCR-free survival probability of 3-year is around 60%, 6-year less than 50%, and 9-year less than 40%.

3.3 Radiotherapy approach, ADT or LN EQD exerts little influence on BCR-free survival

Among the 115 above-mentioned eligible patients, 88 patients received VMAT and the other 27 patients received IMRT. Then we investigated whether different radiotherapy approaches have an influence on the BCR-free survival of the patient cohort. Using the Kaplan-Meier method, the survival curves were plotted for the two groups, and log-rank test showed that there is no survival difference (p = 0.4932; Figure 9). This result indicated that either VMAT or IMRT has a similar influence on the disease control of node-positive prostate cancer patients.

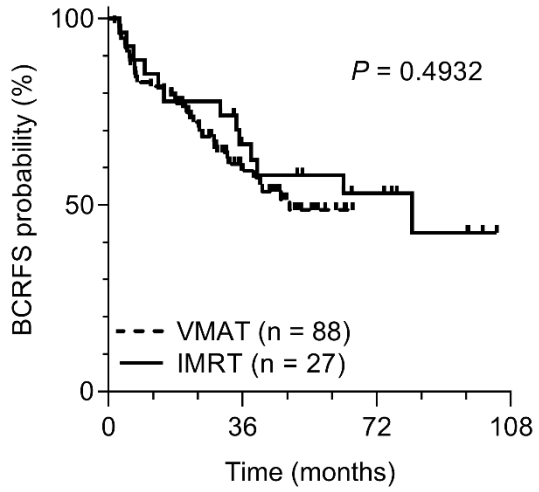

Figure 9: There is no significant survival difference between VMAT and IMRT (p = 0.4932).

Next, we investigated whether ADT has survival benefit for these enrolled patients during RT. ADT was applied to 92 patients, and the other 23 patients did not receive ADT therapy during radiotherapy. Again, the Kaplan-Meier method was performed to draw survival curves for patients who received ADT or did not receive ADT during RT, and log-rank test showed that there is no survival difference between the two groups (p = 0.4932; Figure 10). This finding indicated that addition of ADT to RT did not exert a significant impact on of BCR-free survival of node-positive prostate cancer patients in our patient cohort.

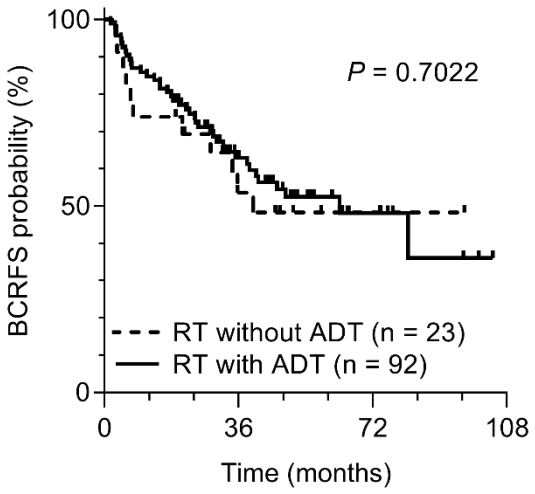

Figure 10: There is no significant survival difference between patients who received or did not receive ADT during RT (p = 0.7022).

Next, we sorted LN EQD2/3 doses of the 115 prostate cancer patients, and we observed that 64.064 Gy is the median value of LN EQD2/3. Among them, 49 patients who received radiation dose of LN EQD 2/3 less than 64.064 Gy were classified into lower dose group. On the other hand, the other 66 patients received radiation dose of LN EQD 2/3 more than 64.064 Gy, and they were categorized into the higher dose group. The Kaplan-Meier method was performed to draw survival curves for lower and higher LN EQD2/3 groups, and log-rank test showed that there is no survival difference between the two groups (p = 0.4573; Figure 11). This result indicated that either LN EQD2/3 more than 64.064 Gy (median value) or less than 64.064 Gy has a similar influence on the BCR-free survival of these node-positive prostate cancer patients.

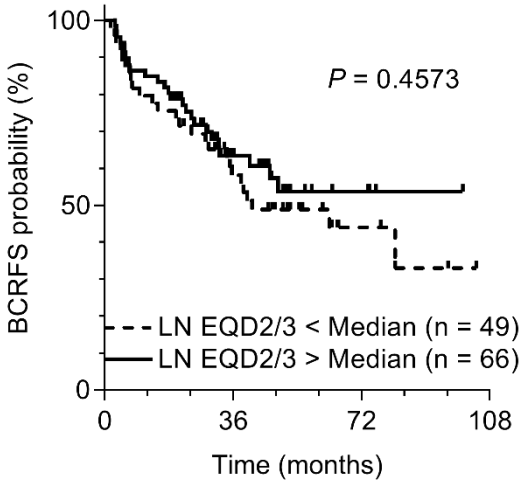

Figure 11: There is no significant survival difference between patients who received lower and higher LN EQD2/3 dose (median as cut-off value, p = 0.4573).

3.4 No significant correlation between Gleason score and LN recurrence

Furthermore, 85 patients after RT without recurrence (any recurrence includes BCR, local recurrence, distant metastasis etc.), with only outfield LN recurrence, or with only infield LN recurrence were extracted for further study. Among them, 12 patients were categorized as only outfield LN recurrence, 10 patients were categorized as only infield LN recurrence, and the rest 63 patients have no recurrence. The distribution of different Gleason score levels was analyzed in LN recurrence, only outfield LN recurrence, and only infield LN recurrence group. Using group t-test analysis, we did not observe significant difference of Gleason score between no recurrence group and only outfield LN recurrence (p = 0.3357) or only infield LN recurrence (p = 0.5588) group. In addition, no significant difference was observed between no recurrence group and LN recurrence (outfield and/or infield) group (p = 0.3018). These results are shown in Figure 12.

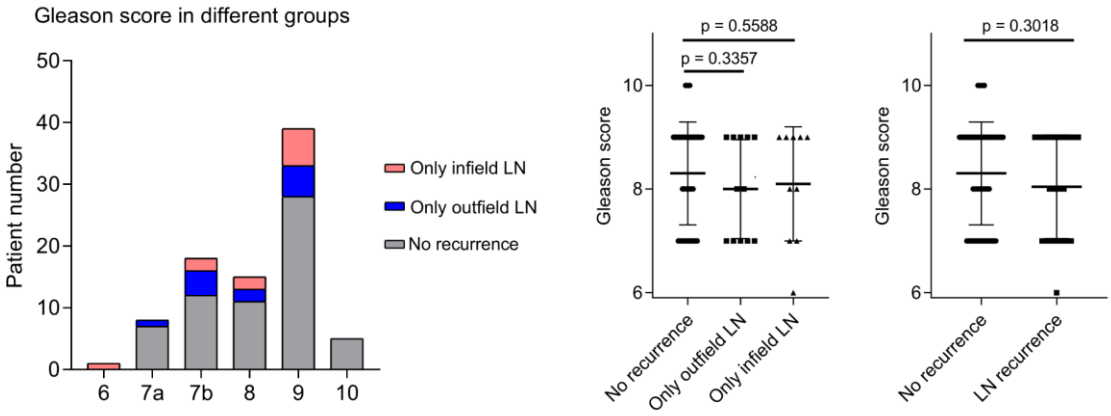

Figure 12: There is no significant difference of Gleason score between no recurrence group and LN recurrence group.

3.5 No significant difference of LN EQD2/1.5 or EQD2/3 among different LN status groups

To investigate the difference of LN EQD among no recurrence group, only outfield group and only infield LN recurrence group, the parameters of LN EQD2/3 and EQD2/1.5 were evaluated among the three groups with different LN status. As shown in Figure 13, t-test analysis indicated that there is no significant difference of LN EQD2/1.5 between no recurrence group and outfield or infield LN recurrence group (no recurrence vs. outfield LN recurrence, p = 0.6678; no recurrence vs. infield LN recurrence, p = 0.6485), and a similar result of LN EQD2/3 was observed among the three groups (no recurrence vs. outfield LN recurrence, p = 0.5918; no recurrence vs. infield LN recurrence, p = 0.7700). These results demonstrated that enough LN EQD doses have little influence on the LN recurrence after RT.

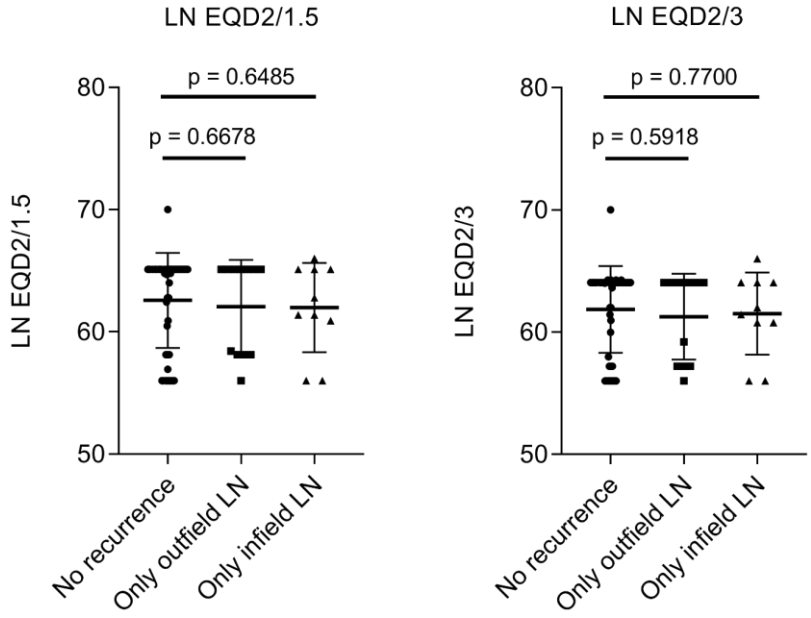

Figure 13: There is no significant difference of LN EQD2/1.5 or EQD2/3 between no recurrence group and LN recurrence group.

3.6 PSA nadir after RT is significantly correlated with LN recurrence

To investigate whether PSA level is correlated with outfield or infield LN recurrence, we recorded PSA values at different stages, including initial PSA when diagnosed, PSA before RT, and PSA nadir after RT. All the PSA values were $\log_{10}(x+1)$ normalized before comparison. Using t-test analysis, we found that there is no significant difference of initial PSA ($p = 0.6529$) or PSA before RT ($p = 0.7225$) between no recurrence group and LN recurrence group. In contrast, PSA nadir after RT was significantly elevated in LN recurrence group compared with no recurrence group ($p < 0.0001$). Then, we analyzed initial PSA, PSA before RT, and PSA nadir after RT among no recurrence, only outfield LN recurrence (annotated as “only outfield LN” in figure), and only infield LN recurrence (annotated as “only infield LN” in figure) groups. Similarly, compared to no recurrence group, no significant difference of initial PSA or PSA before RT was observed in only outfield LN recurrence group (initial PSA: $p = 0.1563$; PSA before RT: $p = 0.4694$) or only infield LN recurrence group (initial PSA: $p = 0.4313$; PSA before RT: $p = 0.8054$), while PSA nadir after RT is significantly elevated in only outfield LN recurrence group ($p < 0.0001$) and only infield LN recurrence group ($p < 0.0001$). These findings demonstrated that among all the PSA values at different stages during or after RT, PSA nadir after RT was proved to serve as a promising indicator for LN recurrence. All the results are shown in Figure 14.

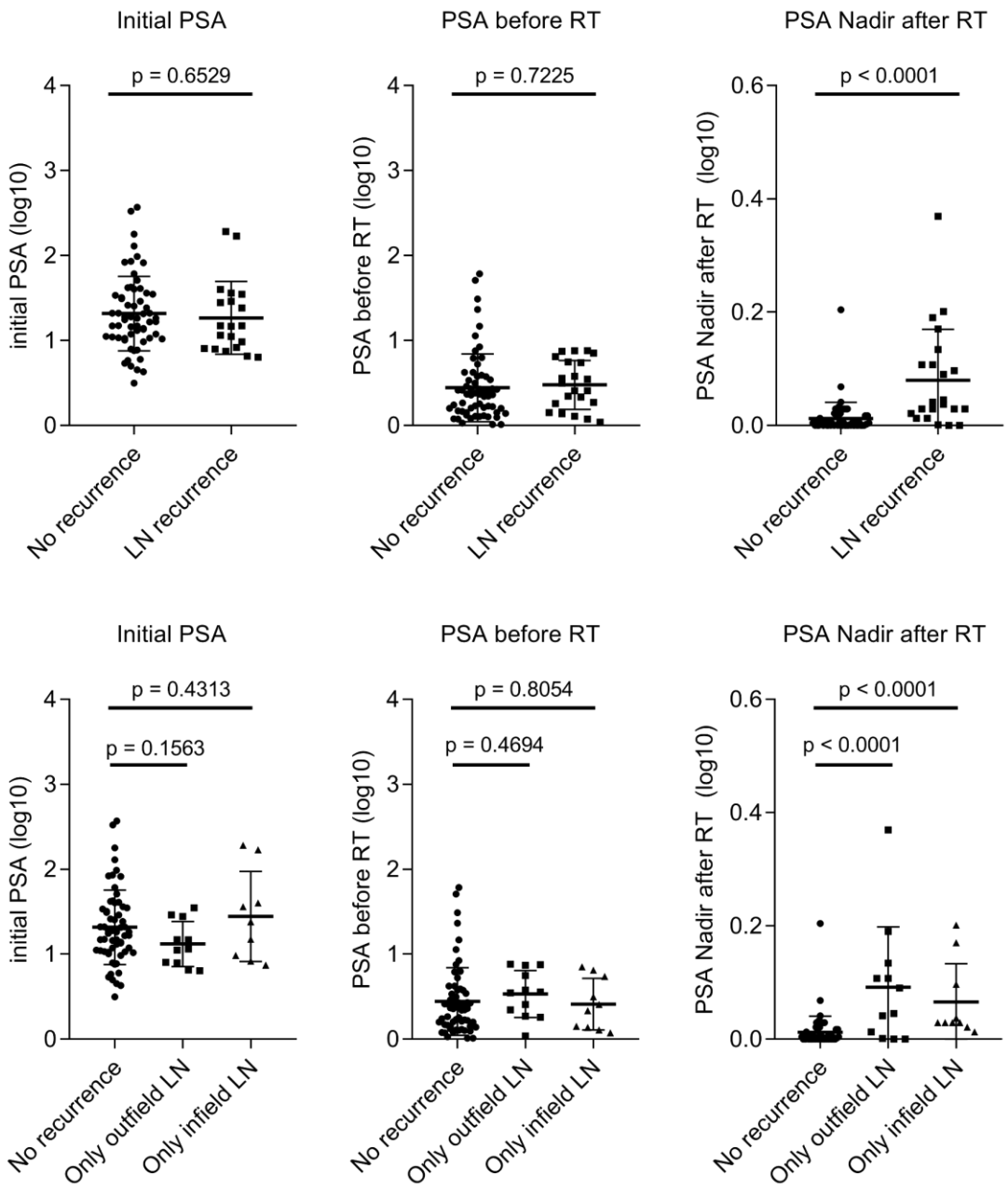

Figure 14: PSA nadir after RT is significantly elevated in outfield or/and infield LN recurrence group compared to patients without recurrence, while no significance was observed in the variables of initial PSA or PSA before RT. All the PSA values were $\log_{10}(x+1)$ normalized.

3.7 RT plus ADT tends to protect patients from LN recurrence

ADT serves as an important adjuvant treatment for prostate cancer patients, and its clinical benefit is still controversial in some previous trials. Based on this fact, we investigated the relationship between ADT and LN recurrence frequency. As shown in Figure 15, in 19 patients without ADT, the number of no recurrence is 11; while in 66 patients with ADT, the number of no recurrence is 52. Because the data distribution is subject to 2 x 2 contingency table, we performed Chi-square test to evaluate their correlation. The result revealed that RT plus ADT might tend to protect patients from LN recurrence (p = 0.067) compared to RT alone, although the p value for the correlation of ADT and LN recurrence did not reach significance.

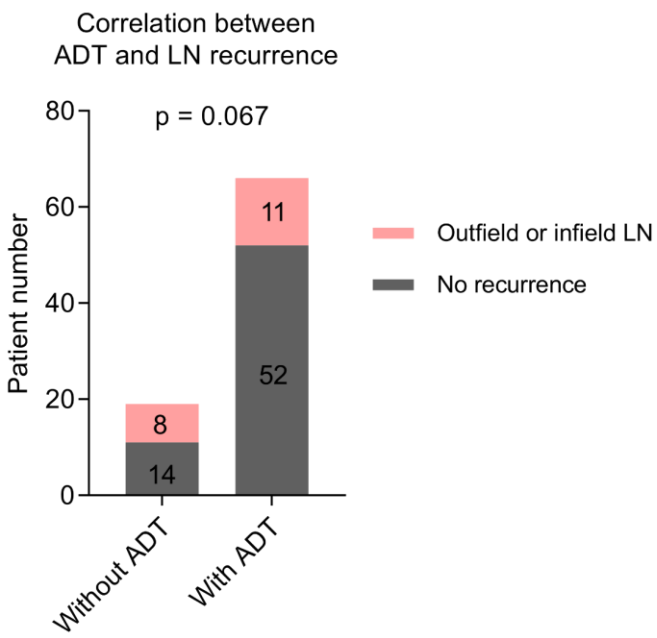

Figure 15: RT plus ADT tends to protect prostate cancer patients from LN recurrence compared to RT alone (p = 0.067).

3.8 Comparison of boost radiation dose of in-situ recurrence LNs and other LNs

We observed seven previously positive LNs still relapsed in situ after boost radiation therapy, and we extracted them for further study. We compared their gross tumor volume (GTV) mean EQD2/1.5 with those of other positive LNs (n = 238). The mean EQD2/1.5 of the seven LNs is 59.78 Gy, while the mean EQD2/1.5 of the other 238 LNs is 63.26 Gy. Using t-test analysis, we found that there is no significant difference of EQD2/1.5 between the two groups, while the difference tends to be significant with a p value of 0.0507 (Figure 16). When removing the lowest EQD2/1.5 of 49.69 Gy (outlier) among the seven in-situ recurrence LNs, we observed that the p value dropped to 0.3426. This finding indicated that a higher dose of boost radiation therapy tends to protect LNs from in-situ recurrence. However, the in-situ group of seven LNs is limited to draw a definite conclusion or to determine a cut-off value to evaluate the risk of in-situ LN recurrence. Therefore, more patients should be enrolled to investigate this issue in further studies.

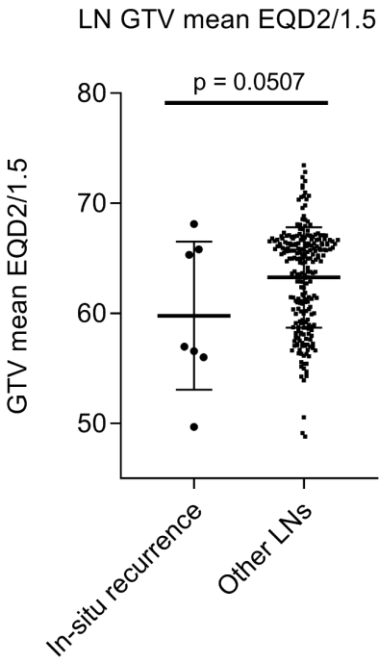

Figure 16: No significant difference of EQD2/1.5 was observed between the in-situ and non-in-situ groups, but the difference tends to be significant with a p value of 0.0507.

3.9 Adverse events analyses

In addition, we recorded the adverse events of the enrolled prostate cancer patients after RT at different follow-up time points, including before RT, 3 months, 15 months, 27 months, and 39 months after RT. The side effects include diarrhea, fecal incontinence, proctitis, erectile dysfunction, dermatitis, urinary incontinence, pollakiuria, nocturia, and dysuria. The adverse event levels were evaluated using Common Terminology Criteria for Adverse Events v4.03 (CTCAE), and these results were summarized in Table 5-9. Throughout the summarization of the side effects of these prostate cancer patients after RT, we observed that adverse events happened more frequently in the short-term follow-up compared to the long-term follow-up, especially erectile dysfunction. Considering the fact that the most common side effects of radical prostatectomy also include urinary incontinence and possible impotence, so the side effects caused by radical prostatectomy and radiotherapy must be intersected, thus we cannot deny the possible overlapping side effects exerted by both surgery and radiotherapy.

Before RT (n=113)

CTCAE	0	1	2	3	Unknown
Diarrhea	108 (95.6%)	4 (3.5%)	1 (0.9%)	0	0
Fecal Incontinence	112 (99.1%)	1 (0.9%)	0	0	0
Proctitis	112 (99.1%)	0	0	0	1 (0.9%)
Erectile dysfunction	16 (14.2%)	9 (8.0%)	19 (16.8%)	38 (33.6%)	31 (27.4%)
Dermatitis	113 (100%)	0	0	0	0
Urinary incontinence	65 (57.5%)	25 (22.1%)	19 (16.8%)	2 (1.8%)	2 (1.8%)
Pollakiuria	103 (91.2%)	7 (6.2%)	3 (2.7%)	0	0
Dysurie	112 (99.1%)	1 (0.9%)	0	0	0

Table 5: Summarization of adverse events before RT (n = 113).

3 month after RT (n=119)

CTCAE	0	1	2	3	Unknown
Diarrhea	104 (87.4%)	11 (9.2%)	4 (3.4%)	0	0
Fecal Incontinence	115 (96.6%)	3 (2.5%)	1 (0.8%)	0	0
Proctitis	110 (92.4%)	7 (5.9%)	1 (0.8%)	1 (0.8%)	0
Erectile dysfunction	14(11.8%)	12 (10.1%)	28 (23.5%)	51 (42.9%)	14 (11.8%)
Dermatitis	117 (98.3%)	1 (0.8%)	0	0	1 (0.8%)
Urinary incontinence	58 (48.7%)	41 (34.4%)	18 (15.1%)	2 (1.7%)	0
Pollakiuria	83 (69.7%)	32 (26.9%)	4 (3.4%)	0	0
Dysurie	113 (95.0%)	4 (3.4%)	2 (1.7%)	0	0

Table 6: Summarization of adverse events in 3 months after RT (n = 119).

15 month after RT (n=78)

CTCAE	0	1	2	3	Unknown
Diarrhea	69 (88.5%)	8 (10.3%)	1 (1.3%)	0	0
Fecal Incontinence	77 (98.7%)	1 (1.3%)	0	0	0
Proctitis	74 (94.9%)	4 (5.1%)	0	0	0
Erectile dysfunction	8 (10.2%)	12 (15.4%)	19 (24.4%)	33 (42.3%)	6 (7.7%)
Dermatitis	78 (100%)	0	0	0	0
Urinary incontinence	38 (48.7%)	23 (29.5%)	16 (20.4%)	1 (1.3%)	0
Pollakiuria	58 (74.4%)	18 (23.1%)	2 (2.6%)	0	0
Dysurie	73 (93.6%)	4 (5.1%)	0	1 (1.3%)	0

Table 7: Summarization of adverse events of total patients in 15 months after RT (n = 78).

27 month after RT (n=52)

CTCAE	0	1	2	3	Unknown
Diarrhea	48 (92.3%)	3 (5.8%)	1 (1.9%)	0	0
Fecal Incontinence	50 (96.2%)	2 (3.8%)	0	0	0
Proctitis	49 (94.2%)	3 (5.8%)	0	0	0
Erectile dysfunction	5 (9.6%)	7 (13.5%)	12 (23.1%)	26 (50%)	2 (3.8%)
Dermatitis	52 (100%)	0	0	0	0
Urinary incontinence	24 (46.2%)	16 (30.8%)	11 (21.2%)	1 (1.9%)	0
Pollakiuria	40	11 (21.2%)	1 (1.9%)	0	0
Dysurie	46 (88.5%)	4 (7.7%)	2 (3.8%)	0	0

Table 8: Summarization of adverse events of total patients in 27 months after RT (n = 52).

39 month after RT (n=19)

CTCAE	0	1	2	3	Unknown
Diarrhea	17 (89.5%)	2 (10.5%)	0	0	0
Fecal Incontinence	18 (94.%7)	0	1 (5.3%)	0	0
Proctitis	19 (100%)	0	0	0	0
Erectile dysfunction	3 (15.8%)	4 (21.1%)	5 (26.3%)	7 (36.8%)	0
Dermatitis	19 (100%)	0	0	0	0
Urinary incontinence	6 (31.6%)	9 (47.4%)	4 (21.1%)	0	0
Pollakiuria	12 (63.2%)	6 (31.6%)	1 (5.3%)	0	0
Dysurie	18 (94.%7)	1 (5.3%)	0	0	0

Table 9: Summarization of adverse events of total patients in 39 months after RT (n = 19).

4. Discussion

Radiation therapy is an effective treatment which uses high-energy rays or particles to kill cancer cells. Various types of radiotherapy have been routinely applied to prostate cancer patients, including External Beam Radiation Therapy (EBRT), Intensity-Modulated Radiation Therapy (IMRT), Volumetric modulated arc therapy (VMAT), Stereotactic Body Radiation Therapy (SBRT), Image-guided Radiation Therapy (IGRT), Brachytherapy, etc.[36] Depending on the stage of the prostate cancer and other clinicopathological factors, radiation therapy might be used: i) As the primary treatment for cancer that is still limited in the prostate gland and with low grade. Cure rates for men with these types of cancers are about the same as those for men treated with radical prostatectomy. ii) As part of the primary treatment (along with ADT) for cancers that have grown outside the prostate gland and into nearby tissues. iii) If the cancer is not resected completely or relapses in the area of the prostate after surgery, or positive lymph nodes are observed in the lymphatic drainage area of prostate after surgery. iv) If the stage is advanced, radiotherapy is used to keep the cancer under control as long as possible and to help prevent or relieve symptoms.

In this study, the retrospective prostate cancer patients mainly received VMAT and IMRT, and our study focused on the clinically or pathologically node-positive prostate cancer patients. For clinically node-positive prostate cancer patients, definitive radiotherapy with ADT is often applied to them. On the other hand, adjuvant radiotherapy with ADT after prostatectomy is offered to patients with pathological node-positive disease. For pathologically node-positive prostate cancer patients after

prostatectomy with pelvic lymphadenectomy, there is still a certain probability that some lymph nodes involved in lymphatic drainage area of prostate develop to positive nodes. Furthermore, patients with node-positive disease tend to have a worse prognosis such as shorter biomedical recurrence-free survival, and the patient management likely needs to be different from single treatment. Some clinical trials compared treatment options for this group of patients. For example, an institutional retrospective study showed that RT plus ADT was significantly correlated with improved overall survival compared with ADT alone, and an analysis of The Surveillance, Epidemiology, and End Results (SEER) Program showed no benefit in overall mortality or cancer-specific mortality of patients who received RT alone.[37] In addition, the Eastern Cooperative Oncology Group (ECOG) 3886 trial established ADT as a standard of care.[38,39] These evidences indicated that RT plus ADT might bring clinical benefits for prostate cancer with positive nodes.

One retrospective study of node-negative patients suggest adjuvant RT plus ADT may be superior to RT alone. Bastide C et al. reported that after a mean follow-up of 60.3 months, compared with the observation group, RT plus ADT treatment significantly improved the BCR-free survival (HR = 0.15; 95% CI = 0.07–0.34; P = 0.001), but RT alone was not (HR = 0.64; 95% CI = 0.36–1.15; P = 0.13).[40] However, till now, no randomized trial or retrospective study has compared RT alone with RT plus ADT for node-positive patients after radical prostatectomy or as primary treatment. In this study, a total of 115 prostate cancer patients with detailed follow-up information were extracted for further investigation. Among the 115 patients, 92 patients received RT

plus ADT, while the rest 23 patients received RT alone. We observed that no significant BCR-free survival difference was observed during a follow-up of 108 months. This result indicated that RT alone might be enough for node-positive prostate cancer patients after radical prostatectomy. However, we have to admit that some deficiencies remain in this study. First, we did not include overall survival as an observational event of these enrolled patients. Second, the retrospective patient cohort is relatively small, which might induce statistical bias. To solve these problems and draw more reliable conclusions, we would like to perform randomized trials and enroll more eligible patients to investigate whether RT plus ADT could significantly improve the BCR-free survival and overall survival of node-positive patients in future studies.

During the treatment and follow-up, PSA values were regularly detected and recorded. To investigate which PSA is significantly correlated with infield or outfield lymph node recurrence, we compared PSA values at three important stages: initial PSA, PSA before RT and PSA nadir after RT. We observed that there is no significant difference of initial PSA and PSA before RT between no recurrence patients and patients with infield or outfield lymph node recurrence. As a contrast, PSA nadir after RT is significantly elevated in both outfield and infield lymph node recurrence patients compared to those without recurrence. These evidences suggested that PSA nadir after RT could serve as a promising predictor for infield or outfield lymph node recurrence, other than initial PSA or PSA before RT. Interestingly, no difference of Gleason score or LN EQD was observed among no recurrence, infield or outfield lymph node recurrence groups.

Although addition of ADT to RT could not improve the BCR-free survival compared to RT alone in our patient cohort, addition of ADT tends to decrease the risk of infield or outfield lymph node recurrence. Considering the statistical p value for the correlation between ADT and lymph node recurrence did not reach significance in our study, this conclusion should be validated in a larger patient cohort. These results revealed that node-positive patients are encouraged to receive RT plus ADT as the best treatment method, at least there is a certain probability to decrease the risk of infield or outfield lymph node recurrence.

Side effects of radiotherapy affect the life quality of prostate cancer patients. Although the modern radiotherapy techniques have greatly reduced the chance of urinary and bowel problems compared to earlier radiation methods, the side effects of radiation therapy should not be ignored. In this study, we evaluated the side effects for as many patients as we can track using the Common Terminology Criteria for Adverse Events v4.03 (CTCAE). In addition, we summarized and analyzed the adverse event frequency, including diarrhea, fecal incontinence, proctitis, erectile dysfunction, dermatitis, urinary incontinence, pollakiuria, nocturia, and dysurie. We observed that adverse events happened more frequently in the short-term follow-up compared to the long-term follow-up, especially erectile dysfunction. We noticed that the most common side effects of radical prostatectomy also include urinary incontinence and possible impotence, so the side effects caused by radical prostatectomy and radiotherapy must be intersected, thus we cannot deny the possible overlapping side effects exerted by both surgery and radiotherapy.

Throughout this study, we would like to put forward two important findings which might be useful for the management of node-positive prostate cancer patients. First, PSA nadir after RT can serve as an ideal predictor which could represent the risk of lymph node recurrence after RT, and significantly higher PSA nadir after RT was observed in outfield or infield lymph node recurrence group compared to those patients without recurrence. Second, compared to RT alone, RT plus ADT has a limited improvement for BCR-free survival in our study, but addition of ADT to RT tends to decrease the risk of lymph node recurrence.

5. Conclusion

In this study, we retrospectively analyzed a total of 126 prostate cancer patients with positive LNs involved in lymphatic drainage area of prostate before radiation therapy in the recent ten years (from 2011 to 2021) in the Department of Radiation Oncology, LMU hospital. Their full-scale clinicopathological features were comprehensively analyzed, including clinical or pathological TNM staging data, Gleason score, radiotherapy approaches, with or without ADT, PSA values (at different stages), lymph node EQD, LN recurrence (outfield or infield) after RT, biochemical recurrence survival information etc. Throughout this study, we can draw two important conclusions: (1) Among all the PSA values at different stages during or after RT, PSA nadir after RT might be a potential indicator for LN recurrence. (2) A higher dose of boost radiation therapy tends to protect LNs from in-situ recurrence, and the cut-off value to evaluate the risk of in-situ LN recurrence should be determined with a larger sample size which includes more eligible LNs.

At last, we have to admit that the enrolled sample size in this study is relatively small, and more eligible patients should be included in the future study to prove the aforementioned findings, thus, to promote the personalized management and precise treatment for LN-positive prostate cancer.

6. Summary

Prostate cancer is the most common malignancy diagnosed in urological system of men worldwide. In particular, prostate cancer patients with positive LNs involved in lymphatic drainage area of prostate always exhibit poor survival despite of comprehensive treatments including RPE, RT, and ADT etc. To evaluate the “real” risk factors for LN recurrence (outfield or infield) after RT, we comprehensively investigated the full-scale clinicopathological features including clinical or pathological TNM staging data, Gleason score, radiotherapy approaches, with or without ADT, PSA values (at different stages), lymph node EQD, LN recurrence (outfield or infield) after RT, biochemical recurrence survival information, and side effects after RT in a total of 126 prostate cancer patients with positive LNs in the aforementioned region. Throughout this study, two important findings were carefully proposed: (1) Compared to other PSA at different stages before, during or after RT, PSA nadir after RT might be a potential indicator for LN recurrence. (2) A higher dose of boost radiation therapy tends to protect LNs from in-situ recurrence. However, to make our conclusions more robust, more eligible patients should be enrolled in future studies.

7. Abbreviations

UICC: Union International Cancer Control

PSA: prostate-specific antigen

TNM: Tumor-Node-Metastasis

LN: lymph node

BCR: biochemical recurrence

TRUS: Transrectal Ultrasound

DRE: digital rectal examination

GS: Gleason score

RPE: radical prostatectomy

LAE: lymphadenectomy

RT: radiation therapy

EQD: equivalent dose

ART: adjuvant radiotherapy

SRT: salvage radiotherapy

AS: active surveillance

WW: watchful waiting

ADT: androgen deprivation therapy

LH: luteinizing hormone

GnRH: releasing hormone gonadotrophin-releasing hormone

IMRT: intensity-modulated radiation therapy

VMAT: volumetric modulated arc therapy

IGRT: image-guided radiation therapy

SBRT: stereotactic body radiation therapy

GTV: gross tumor volume

AE: adverse events

CTCAE: Common Terminology Criteria for Adverse Events

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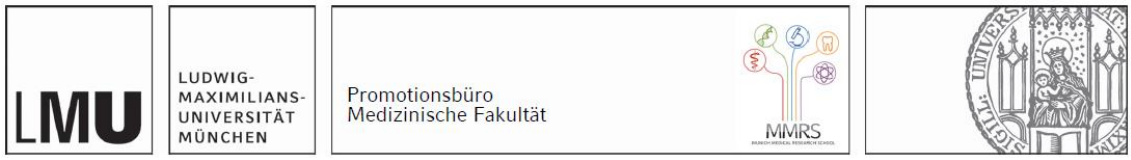

Affidavit

SUN, Jing

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I hereby declare, that the submitted thesis entitled:

Dosimetric analysis of radiotherapy in prostate cancer patients with pelvic or paraaortic lymph nodes involvement

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Munich, 02/09/2021 Jing Sun