Research Article **Open Access**

Endoscopic, Transperitoneal Radical Prostatectomy with 3.0-T mpMRI Stratifies Patients with Advanced Prostate Cancer

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Abstract

Objective: Recent years have brought a significant shift in case selection for the surgical treatment of prostate cancer (PCa). Primary surgical management is increasingly implemented in more aggressive tumors, however the role of radical prostatectomy (RP) in advanced cases remains controversial. The aim of the present study is to explore cancer diversity in patients who were subjected to endoscopic, transperitoneal RP due to very high-risk advanced PCa.

Methods: Our database was screened for prostate cancer patients with clinically diagnosed seminal vesicles infiltration and/or invasion of other adjacent structures (cT3b-4 N0) and/or suspected nodal involvement (cT1-4 N1) who underwent ERP. Twenty cases were identified: 11 patients with cT3b-4 N0 disease and 9 patients with suspected nodal involvement. The preoperative tumor stage was assessed with the use of multiparametric magnetic resonance (mpMRI) in all cases.

Results: Although the accuracy of mpMRI in the assessement of local tumor stage was 85%, the lymph node status was properly assessed preoperatively in 45% cases only. The pT3b-4 PCa was diagnosed in 13 cases (65%). Of them, 9 had lymph nodes metastases. Three patients (15%) were diagnosed with pT3a cancer, among them nodal metastases were confirmed in 2 cases. In the remaining 4 patients (20%), the tumor was confined to the prostate but in 1 of them pelvic lymph nodes were involved. Early, postoperative PSA was lower than 0.2 ng/ml in 13 patients (65%). Seventeen patients (85%) received additional treatment: androgen deprivation therapy in 7 cases (35%), radiation therapy in 10 cases (50%). No pad use was declared by 14 patients (70%).

Conclusion: Radical prostatectomy thoroughly stratifies patients diagnosed with advanced prostate cancer. In more than a half of cases the clinical stage differs from the pathological disease status. Correct, postoperative prostate cancer stratification allows to personalize multidisciplinary treatment to reduce toxicity and improve oncological outcome.

Keywords: Prostate cancer; Radical prostatectomy; Seminal vesicles infiltration; Nodal involvement; Magnetic resonance

Introduction

Prostate cancer (PCa) remains the second most common malignancy diagnosed in males worldwide with more than a million cases diagnosed in 2012 [1]. The mainstay therapy for organ confined disease is radical prostatectomy (RP). Throughout the recent decades we have witnessed significant shift in case selection for the surgery. In the past, RP was thought to be a treatment option in patients with organ confined disease only. Currently many patients with the lowest risk of progression and the disease limited to the gland are successfully managed by active surveillance [2], selected men from intermediate-risk group are considered eligible for focal therapy [3] and radical prostatectomy is thought to be a reasonable first step in patients with clinical signs of extracapsular extension (ECE). However, both understaging of organ confined disease and overstaging of clinical locally advanced PCa are common and found in as much as 43–75% and 30% respectively [4].

After RP, additional radiation is discussed when adverse pathology including positive surgical margins (PSMs) is found whereas surgery remains the only treatment modality in many of those who were deemed to have locally advanced PCa and were ultimately diagnosed with organ confined disease with undetectable prostate specific antigen (PSA). Early androgen deprivation is concerned when regional lymph nodes are found to be infiltrated.

Although expanding, the role of primary surgery in patients with cancer clinically invading prostate adjacent structures or pelvic lymph nodes is not fully elucidated. According to European Association of Urology Guidelines on Prostate Cancer only highly selected patients with high-risk locally advanced PCa may be offered radical prostatectomy within a multimodality setting, at the same time, radiation therapy together with long-term androgen deprivation is recommended in patients with either clinically involved lymph nodes or very high-risk locally advanced (cT3b-cT4) PCa without recognition of any differences between the two categories [5]. In the meantime, novel diagnostic techniques were introduced to improve prostate cancer staging including multi-parametric magnetic resonance imaging (mpMRI).

The major goal of the present study is to explore prostate cancer diversity in patients with clinically seminal vesicles infiltration and/or invasion of other adjacent structures (cT3b-4 N0) and/or suspected nodal involvement (cT1-4 N1) who were subjected to endoscopic, transperitoneal radical prostatectomy (ERP) with extended, pelvic lymphadenectomy preceded with 3.0-T mpMRI. Furthermore, we aim to analyze early oncological and functional results of surgery in this group of patients.

Materials and Methods

Our database was screened for patients subjected to endoscopic radical prostatectomy with extended pelvic lymph node dissection performed due to advanced prostate cancer. Twenty cases were identified that included 11 patients with cT3b-4 N0 disease and 9 patients with suspected nodal infiltration (5 with cT2a-3a PCa and 4 with cT3b-4 PCa). Two patients underwent the initial prostate biopsy due to abnormal findings in digital rectal examination (DRE), in the remaining 18 patients the diagnosis was initiated because of the rise in PSA. Transrectal, multicore prostate biopsy under ultrasound guidance was utilized in all cases. The stage of PCa and the status of regional lymph nodes were ultimately established with 3.0-T mpMRI and bone metastases were excluded after technetium based scans in every patient. Lymph nodes were concerned involved by PCa when their maximum diameter was greater or equal to 10 mm. The decision to incorporate computed tomography (CT) scans of the abdomen and the pelvis were left to the discretion of treating physician and were used variably in some equivocal cases in which the diagnosis of metastases was ambiguous. The PSA density (PSAD) was calculated based on the prostate volume measured by mpMRI.

Patients were counselled before the operation within a multidisciplinary team in regard to their disease status and alternative treatment options. They were informed on high likelihood of biochemical failure after the initial surgical treatment and the need for additional therapy. All patients signed informed consent and decided to precede with surgery. Endoscopic, transperitoneal radical prostatectomy with extended, pelvic lymphadenectomy was performed. Common, external and internal iliac, presacral and obturator lymph nodes were removed from both sides in every patient. After the operation close follow-up was implemented. Every patient had his early postoperative PSA level examined, the time of examination ranged from two to three months. Further diagnostic and therapeutic decisions were made individually on the basis of early PSA level and the official pathological report.

The clinical stage and the biopsy Gleason score were compared with corresponding postoperative entities. Surgical margins and nodal status were assessed by experienced uro-pathologist. Early postoperative PSA and the rates of biochemical failure during the first year of follow up were examined and consequently the number of patients that needed additional treatment and its quality were evaluated as well. Patients were asked to report their continence. No pad use was recognized as the definition of complete continence.

Results

Pathological examination revealed infiltration of either seminal vesicles or other adjacent structures (pT3b-4) in 13 cases (65%). Of them, 9 (69%) turned out to have lymph nodes metastases. Three patients (15%) were diagnosed with extracapsular extension without any signs of infiltrating of adjacent structures (pT3a), among them nodal metastases were confirmed in 2 cases (66.7%). In the remaining 4 men (20%), the tumor was found to be confined to the prostate (pT2a-2c), however in 1 of them (25%) pelvic nodes were involved. All clinical data is delineated in Table 1.

Preop. stage	Preop. Gl.s.	Age	PSA (ng/ml)	PSAD	DRE	Postop. Gl.s.	Postop. stage	No of nodes (positive/removed)	Surgical margins
cT3b N0									
	7(3+4)	73	10	0.41	+	7(4+3)	pT3a pN0	(0/16)	-
		62	72	1.71	-	7(4+3)	pT3b pN0	(0/19)	+
		59	43.6	1.89	+	9(4+5)	pT3b pN0	(0/20)	+
	7(4+3)	65	7.8	0.26	+	7(4+3)	pT3b pN1	(1/23)	-
		63	25	0.58	+	7(4+3)	pT3b pN1	(2/22)	-
		61	13.8	0.43	+	7(3+4)	pT3b pN1	(3/30)	+
	8(4+4)	54	39	1.39	+	8(4+4)	pT3b pN1	(18/28)	-
	9(4+5)	54	7	0.15	-	9(4+5)	pT3b pN0	(0/23)	+
		66	6.8	0.3	+	9(4+5)	pT3b pN1	(6/19)	+
		54	13.9	0.92	+	9(4+5)	pT3b pN1	(8/18)	-
cT4 N0									
	8(4+4)	44	12.2	0.46	+	9(4+5)	pT4 pN1	(3/23)	+
cN1									
	cT2a 6(3+3)	62	15.8	0.28	-	6(3+3)	pT2a pN0	(0/33)	-

	cT3b	7(3+4)	50	5.8	0.05	+	7(3+4)	pT2c pN0	(0/29)	-
	cT3b		56	12.6	0.38	+	8(4+4)	pT3b pN1	(1/23)	+
	cT2b	7(4+3)	69	3.1	0.1	+	10(5+5)	pT2c pN0	(0/44)	-
	cT3a		62	27	0.77	+	7(4+3)	pT3a pN1	(2/20)	+
	cT3b	8(3+5)	46	3.6	0.12	+	9(4+5)	pT3b pN1	(5/34)	+
	cT2b	8(4+4)	64	13	0.17	+	8(4+4)	pT2b pN1	(4/25)	-
	cT3a		66	11.5	0.5	+	8(4+4)	pT3a pN1	(1/28)	-
	cT4	10(5+5)	60	7.2	0.11	+	9(5+4)	pT4 pN0	(0/10)	+
Abbreviations: PSA – prostate specific antigen, PSAD – prostate specific antigen density, DRE – digital rectal examination, Gl.s. – Gleason score, preop. – preoperative, postop. – postoperative, No – number										

Table 1: Patient characteristics and early postoperative results.

Clinical local tumor stage of PCa was confirmed by the pathological examination of the specimen in 17 patients (85%). One case (5%) of understaging was noted and in 2 cases (10%) the tumor stage was preoperatively overestimated. The mpMRI detected ≥T3b PCa with the sensitivity of 100% and specificity of 71%. Corresponding positive predictive value (PPV) and negative predictive value (NPV) were 87% and 100% respectively. In the ROC curve analysis the area under the curve (AUC) of mpMRI in detecting advanced PCa reached 0.8.

Of 9 patients with clinically suspected nodal disease, lymph nodes metastases were discovered in 5 cases (55.6%). In remaining 4 patients (44.4%) the lymph nodes were not involved. More importantly, out of 11 patients with very high-risk locally advanced PCa but clinically intact pelvic nodes (cN0), 7 (63.6%) turned out to be node-positive. In regard to nodal metastases detection, sensitivity, specificity, PPV and NPV of mpMRI were 42%, 50%, 56%, 36% respectively. In the ROC curve analysis the AUC of mpMRI in detecting nodal metastases was 0.5.

Positive surgical margins were found in 10 cases (50%). After reevaluation, they were described as extensive (>3 mm) or multifocal in 7 cases.

Significant rate of discrepancies between the preoperative and postoperative Gleason score (Gl.s.) was observed. The vast majority of patients had an aggressive tumor with the predominant Gleason Pattern ≥ 4 in 17 (85%) of them. Preoperative Gl.s. remained unchanged after surgery in only 11 cases (55%), whereas in the remaining 7 (35%) and 2 (10%) cases, Gl.s. was under and overestimated accordingly.

The mean follow-up time was 118.8 weeks (median 123.8). As shown in Table 2, early PSA level was lower than 0.2 ng/ml in 13 patients (65%) including 7 with PSMs. Out of these 13 men with favorable early PSA level 7 (53.8%) were diagnosed with biochemical failure during the first year of follow up. Among them only three had PSMs after ERP. Patients with specimen confined disease (SCD) and early, postoperative PSA lower than 0.2 ng/ml had lower PSA and PSAD values and tended to have less aggressive disease (Table 3). Seventeen patients (85%) received additional treatment: 7 patients (35%) started early androgen deprivation therapy (ADT) with LHRH analog or underwent bilateral orchiectomy as the only modality, 10 patients (50%) underwent external beam radiation therapy (EBRT) – in 8 cases combined with ADT. In 4 cases the irradiation was used as an adjuvant treatment, in the remaining 6 cases salvage radiation was implemented. One patient refused to undergo any form of additional treatment despite biochemical failure. During follow up, 14 patients (70%) declared complete urinary continence recovery.

Postop. stage	Postop. Gl.s.	PSAD	Surgical margins	Early postop. PSA (ng/ml)	Biochemical failure during first year of follow up	ADT/ bilateral orchiectomy	Adjuvant EBRT	Salvage EBRT	Urinary continence recovery
pN0									
	pT2a	6(3+3)	0.28	-	<0.2	-	-	-	-	+
	pT2c	7(3+4)	0.05	-	<0.2	-	-	-	-	+
		10(5+5)	0.1	-	<0.2	+	+	-	-	+
	pT3a	7(4+3)	0.41	-	<0.2	+	+	-	+	-
	pT3b	9(4+5)	1.89	+	<0.2	-	-	+	-	-
		9(4+5)	0.15	+	<0.2	-	-	-	+	+

		7(4+3)	1.71	+	<0.2	-	+	+	-	+
	pT4	9(5+4)	0.11	+	<0.2	+	+	+	-	+
pN1										
	pT2b	8(4+4)	0.17	-	≥0.2	+	+	-	-	-
	pT3a	8(4+4)	0.5	-	≥0.2	+	+	-	-	-
		7(4+3)	0.77	+	≥0.2	+	+	-	-	+
	pT3b	7(4+3)	0.58	-	<0.2	+	-	-	-	+
		7(4+3)	0.26	-	<0.2	+	+	-	+	+
		8(4+4)	1.39	-	≥0.2	+	+	-	-	+
		9(4+5)	0.92	-	≥0.2	+	+	-	-	+
		7(3+4)	0.43	+	<0.2	+	+	-	+	-
		9(4+5)	0.12	+	<0.2	+	+	-	+	+
		8(4+4)	0.38	+	<0,2	-	+	+	-	-
		9(4+5)	0.3	+	≥0,2	+	+	-	-	+
	pT4	9(4+5)	0.46	+	≥0,2	+	+	-	+	+

Abbreviations: postop. – postoperative, Gl.s. – Gleason score, PSA - prostate specific antigen, PSAD – prostate specific antigen density, ADT – androgen deprivation therapy, EBRT – external beam radiation therapy

Table 2: Biochemical failure and additional treatment application rates during the follow up.

	Specimen confined disease with early PSA < 0.2 ng/ml (4 cases)	Non-specimen confined disease (16 cases)
	mean (median)	
Age (years)	63.5 (65.5)	58.5 (60.5)
PSA (ng/ml)	8.7 (7.9)	19.7 (12.8)
PSAD	0.21 (0.19)	0.63 (0.44)
Gl.s. (biopsy)	6.75 (7)	7.87 (8)
Predominant Gl. p.	3.25 (3)	3.81 (4)
	number (percentage) of patients	
cT2a-2c	2 (50%)	1 (6.25%)
cN1	3 (75%)	6 (37.5%)

Abbreviations: PSA – prostate specific antigen, PSAD – prostate specific antigen density, Gl.s. – Gleason score, Gl.p. – Gleason pattern, cT – local tumor stage, cN – nodal stage

Table 3: Clinical characteristics of patients with specimen confined PCa (pN0, R0) and low, early postoperative PSA and those with non-specimen confined disease or detectable postoperative PSA.

Discussion

Our observations confirm the presence of significant diversity in regard to the stage and the grade of prostate cancer clinically deemed to invade either seminal vesicles or other adjacent structures and pelvic lymph nodes that would be otherwise a subject of hormonal therapy only or hormonal therapy combined with external beam irradiation. This diversity is followed by variety of additional management implemented after surgery in particular cases to provide the best possible outcome. The accuracy of modern imaging to correctly assess regional lymph nodes is far from being acceptable. On the contrary we

noticed very high sensitivity and positive predictive value of mpMRI in the recognition of periprostatic structures infiltration.

The discrepancies between the preoperative and postoperative tumor stage were observed by other authors, both for the local tumor stage and lymph node (LN) involvement. A study by Joniau et al. showed that among 51 patients with cT3b-4 N0 M0 prostate cancer who underwent surgical treatment overstaging was relatively frequent (37.2%) and that four patients (7.8%) turned out to have an organ confined disease [6]. This data speaks in favor of performing surgery in advanced cases as the chance of achieving complete cancer control is encouraging. In this study, however, the local tumor stage was assessed by DRE only. Currently, patients with clinically advanced disease are more frequently diagnosed with mpMRI. In the study by Park et al. 3.0-T mpMRI was able to properly define the local tumor stage in 261 out of 353 patients (73.9%) diagnosed with PCa, the overstaging occurred in 43 cases only (12.2%) [7]. In this study the sensitivity, specificity, PPV and NPV for predicting T3 stage were 55.9%, 82.2%, 59.1%, 80.2% respectively. Not surprisingly, the sensitivity of MRI in predicting extracapsular extension tended to increase from low-risk to high-risk PCa groups. It barely exceeded 33% in the former group, whereas it mounted to 80% in the latter group. In another study [8] 3.0-T mpMRI supported correct assessment of local tumor stage in 37 out of 47 patients (78.7%), the overstaging was relatively rare, it occurred in 3 men only (6.3%). In this study seven patients were diagnosed with pT3 PCa, no patient turned out to have pT4 disease. The calculated sensitivity, specificity, PPV and NPV in predicting extracapsular extension were 57.1%, 95%, 66.6%, 92.6% respectively and the overall accuracy for detecting ECE was 89.3%. These studies corroborate our results and add evidence to confirm significant accuracy of mpMRI in local staging of high risk prostate cancer. Apart from improved resolution of T2 weighted images (T2WI), modern MRI machines provide multiple functional techniques including diffusion weighted imaging (DWI) and dynamic contrast enhancement (DCE). According to recent meta-analysis by de Rooij et al. sensitivity and specificity of MRI in seminal vesicles assessment were 58% and 96% respectively [9]. The sensitivity was relatively poor and lower than presented in our study, however less than a half of the studies included into analysis incorporated one or more additional functional techniques combined with T2WI. Corresponding values for 3.0-T multiparametric MRI were 73% and 95% accordingly. In summary, joint analysis of T2WI with DWI and DCE makes the mpMRI an accurate tool for preoperative local prostate cancer staging, especially when images are analyzed by experienced radiologist.

In contrast to local staging, accuracy of mpMRI in evaluation of regional lymph nodes in PCa is not satisfactory. This phenomenon may be explained by the lack of specific hallmarks that would stigmatize lymph nodes infiltrated by the cancer. Instead, only the size of the lesion is used to determine the presence of PCa nodal metastases. Not surprisingly, this philosophy, as shown by our results, is associated with high rate of false-positive results. In a meta-analysis by Hövels et al. the sensitivity and specificity of MRI in detecting nodal metastases were 39% and 82% respectively [10]. The size cut-point used to define lymph node involvement in the analysis ranged from 5 mm to 15 mm. Furthermore, adding functional sequences into MRI protocol does not substantially improve N-staging. According to study by von Below et al. sensitivity and specificity of detecting nodal metastases by MRI with DWI were 55% and 90% respectively [11]. Although these results are optimistic, mpMRI cannot replace or even constrain pelvic lymphadenectomy in selected PCa patients. Conventional CT scan is not significantly better than MRI in this respect. Even highly sophisticated, 68Gallium-PSMA Positron Emission Tomography/CT detects LN metastases with sensitivity of 64% [12]. Low accuracy of all presented modalities in the detection of lymph node involvement argues against their utilization in preoperative N-staging.

Patients with locally advanced PCa and regional lymph nodes involvement remain at significant risk of early biochemical failure and disease progression after initial management. Instead of surgery, most of them are subjected to androgen deprivation therapy (ADT) combined with radiation. This strategy has been proven effective in randomized trials [13-15]. Our study shows, however, that this group of patients is very heterogeneous. In our setting, radical prostatectomy is not concerned a treatment modality only but it also appears to be a highly reliable staging procedure. Presence and quality of extraprostatic extension or positive surgical margins, as well as the number of involved lymph nodes are precisely evaluated by the pathologist. In the study by Joniau et al. despite cT3b-4 N0 M0 prostate cancer, nearly a quarter of patients remained free of any additional treatment after surgery [6]. In our group, 3 (15%) patients preoperatively classified as having advanced prostate cancer were found to have disease confined to the gland (pT2a-2c N0). Two of them were managed with surgery alone, only one experienced biochemical failure and salvage treatment was implemented. All three regained complete continence. If primary surgery would not be implemented they would irrevocably receive EBRT together with long-term ADT. In those with adverse pathology, in particular in those with PSMs after RP, adjuvant radiation may improve biochemical free survival or even overall survival [16]. However, PSM that is not established but focal (<3 mm) may not necessarily portend unfavorable outcomes when compared to negative surgical margins in patients after RP [17]. Moreover, increasing evidence suggests that early salvage radiotherapy provides cancer specific and all-cause mortality similar to adjuvant irradiation regardless of the stage of PCa [18]. Among different clinical features, low PSA, low PSAD and predominant Gleason pattern 3 increase the likelihood of favorable outcome [19,20]. Majority of our patients who had early, postoperative PSA lower than 0.2 ng/ml were diagnosed with biochemical failure during the first year of follow up. Similarly, in the study by Hegemann et al. [21] nearly half of 71 patients with pT3a N0 PCa and microscopic PSMs with undetectable PSA after RP experienced PSA progression within the median follow up of 80 months. Patients found with positive lymph nodes benefit from early ADT. According to the landmark study of Messing et al. [22] early hormonal therapy prolongs overall survival in those with pN+ disease after RP but the number of lymph nodes involved matters [23]. In our series, seven (35%) patients were diagnosed with more than two positive lymph nodes and started early ADT, in five of them early postoperative PSA was elevated and exceeded 0.2 ng/ml. Altogether, these studies support our results and suggest that patients with advanced prostate cancer after RP may benefit from a variety of therapeutic approaches and application of one strategy to all of them results in substantial mistreatment. Once castration resistance is diagnosed, previous local therapy has significant impact on quality of life associated with lower urinary tract symptoms. It has been shown that radical prostatectomy is associated with lower rate of local complications when compared to previous radiotherapy [24]. We belive radical prostatectomy should become the first step of multimodality treatment of patients with advanced prostate cancer.

Morbidity remains the major concern related to radical prostatectomy in advanced PCa. Surprisingly the functional outcomes

after endoscopic RP in our cohort are very promising. Most of the patients reported complete urinary continence recovery. None of those who did not report continence recovery has required surgical management of urinary incontinence so far. Nonetheless, the primary goal of RP in the very high-risk PCa is complete removal of cancerous tissue from the pelvis, therefore extensive surgery without neurovascular bundles sparring approach is implemented. In addition, recent study by Zelefsky et al. [25] showed that in comparison to brachytherapy and high-dose intensity-modulated radiotherapy, RP in patients with clinically localized prostate cancer was associated with greater incontinence rates at 4 years of follow-up but it was also associated with less urinary irritation and that there were no significant differences among the three modalities in overall urinary function or bother.

We acknowledge several limitations of our study. The number of patients is low and the follow up is short, however we were able to present significant diversity in clinically similar cases in regard to pathology and early biochemical outcomes. We will continue our surveillance and expand the group of patients to explore long term results of surgery in the very high-risk PCa. Another drawback of the study results from the combination of patients with clinically locally advanced disease with those with suspected nodal involvement, yet it reflects the treatment policy of delivering radiation therapy together with androgen deprivation in both entities in a similar fashion. We have shown that the two groups of patients are extremely heterogeneous and should be evaluated separately.

Conclusions

Radical prostatectomy thoroughly stratifies patients diagnosed with very high-risk, locally advanced prostate cancer and prostate cancer suspected to invade regional lymph nodes. In more than a half of cases the clinical stage appears to differ from the pathological status of the disease. Majority of patients experience biochemical failure and require additional treatment. However, due to significant over staging, some males are cured and left with surgery alone, while others are counseled to tailor adjuvant or salvage management. The solid base for the discussion is provided by histological evaluation of specimen removed by urologist. The exact value of specific additional treatment modalities that supplement RP remains to be elucidated. Furthermore, we should continue our efforts to improve the functional outcomes of RP, keeping the rates of positive surgical margins as low as possible.

References

1. World Health Organization (2012) International Agency for Research on Cancer.
2. Klotz L, Vesprini D, Sethukavalan P, Jethava V, Zhang L, et al. (2015) Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. J Clin Oncol 33: 272-277.
3. Donaldson IA, Alonzi R, Barratt D, Barret E, Berge V, et al. (2015) Focal therapy: patients, interventions, and outcomes--a report from a consensus meeting. Eur Urol 67: 771–777.
4. van den Ouden D, Schröder FH (2000) Management of locally advanced prostate cancer 1. Staging, natural history, and results of radical surgery. World J Urol 18: 194-203.
5. European Association of Urology (2016) Guidelines on Prostate Cancer.
6. Joniau S, Hsu CY, Gontero P, Spahn M, Van Poppel H (2012) Radical prostatectomy in very high-risk localized prostate cancer: long-term outcomes and outcome predictors. Scand J Urol Nephrol 46: 164-171.
7. Park BH, Jeon HG, Jeong BC, Seo SI, Lee HM, et al. (2014) Influence of magnetic resonance imaging in the decision to preserve or resect neurovascular bundles at robotic assisted laparoscopic radical prostatectomy. J Urol 192: 82-88.
8. Couñago F, Recio M, Del Cerro E, Cerezo L, Díaz Gavela A, et al. (2014) Role of 3.0 T multiparametric MRI in local staging in prostate cancer and clinical implications for radiation oncology. Clin Transl Oncol 16: 993-999.
9. de Rooij M, Hamoen EH, Witjes JA, Barentsz JO, Rovers MM (2016) Accuracy of magnetic resonance imaging for local staging of prostate cancer: a diagnostic meta-analysis. Eur Urol 70: 233-245.
10. Hövels AM, Heesakkers RA, Adang EM, Jager GJ, Strum S, et al. (2008) The diagnostic accuracy of CT and MRI in the staging of pelvic lymph nodes in patients with prostate cancer: a meta-analysis. Clin Radiol 63: 387-395.
11. von Below C, Daouacher G, Wassberg C, Grzegorek R, Gestblom C, et. al. (2016) Validation of 3 T MRI including diffusion-weighted imaging for nodal staging of newly diagnosed intermediate- and high-risk prostate cancer. Clin Radiol 71: 328-334.
12. van Leeuwen PJ, Emmett L, Ho B, Delprado W, Ting F, et al. (2016) Prospective evaluation of 68Gallium-PSMA positron emission tomography/computerized tomography for preoperative lymph node staging in prostate cancer. BJU Int 13540.
13. Mason MD, Parulekar WR, Sydes MR, Brundage M, Kirkbride P, et al. (2015) Final report of the intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer. J Clin Oncol 33: 2143-2150.
14. Mottet N, Peneau M, Mazeron JJ, Molinie V, Richaud P (2012) Addition of radiotherapy to long-term androgen deprivation in locally advanced prostate cancer: An open randomised phase 3 trial. Eur Urol 62: 213-219.
15. Bolla M, Collette L, Blank L, Warde P, Dubois JB, et al. (2002) Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. Lancet 360: 103-106.
16. Thomson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, et al. (2009) Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. J Urol 181: 956-962.
17. Dobruch J, Nyk L, Skrzypczyk M, Chłosta P, Dzik T, et al. (2012) Clinical significance of surgical margin status in patients subjected to radical prostatectomy. Cent European J Urol 65: 195-199.
18. Briganti A, Wiegel T, Joniau S, Cozzarini C, Bianchi M, et al. (2012) Early salvage radiation therapy does not compromise cancer control in patients with pT3N0 prostate cancer after radical prostatectomy: results of a match-controlled multi-institutional analysis. Eur Urol 62: 472-487.
19. Jones TD, Koch MO, Bunde PJ, Cheng L (2006) Is prostate-specific antigen (PSA) density better than the preoperative PSA level in predicting early biochemical recurrence of prostate cancer after radical prostatectomy? BJU Int 97: 480-484.
20. Amin A, Partin A, Epstein JI (2011) Gleason score 7 prostate cancer on needle biopsy: relation of primary pattern 3 or 4 to pathological stage and progression after radical prostatectomy. J Urol 186: 1286-1290.
21. Hegemann NS, Morcinek S, Buchner A, Karl A, Stief C, et al. (2016) Risk of biochemical recurrence and timing of radiotherapy in pT3a N0 prostate cancer with positive surgical margin : A single center experience. Strahlenther Onkol 192: 440-448.
22. Messing EM, Manola J, Yao J, Kiernan M, Crawford D (2006) Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. Lancet Oncol 7: 472-479.
23. Briganti A, Karnes JR, Da Pozzo LF, Cozzarini C, Gallina A (2009) Two positive nodes represent a significant cut-off value for cancer specific survival in patients with node positive prostate cancer. A new proposal based on a two-institution experience on 703 consecutive N+ patients treated with radical prostatectomy, extended pelvic lymph node dissection and adjuvant therapy. Eur Urol 55: 261-270.

24. Won AC, Gurney H, Marx G, De Souza P, Patel MI (2013) Primary treatment of the prostate improves local palliation in men who ultimately develop castrate-resistant prostate cancer. BJU Int 112: 250-255.

25. Zelefsky MJ, Poon BY, Eastham J, Vickers A, Pei X, et al. (2016) Longitudinal assessment of quality of life after surgery, conformal brachytherapy, and intensity-modulated radiation therapy for prostate cancer. Radiother Oncol 118: 85-91.