Advances in Urology

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# Editorial Board

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*Review Article*

# HDR Brachytherapy in the Management of High-Risk Prostate Cancer

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High-dose-rate (HDR) brachytherapy is used with increasing frequency for the treatment of prostate cancer. It is a technique which allows delivery of large individual fractions to the prostate without exposing adjacent normal tissues to unacceptable toxicity. This approach is particularly favourable in prostate cancer where tumours are highly sensitive to dose escalation and to increases in radiotherapy fraction size, due to the unique radiobiological behaviour of prostate cancers in contrast with other malignancies. In this paper we discuss the rationale and the increasing body of clinical evidence for the use of this technique in patients with high-risk prostate cancer, where it is combined with external beam radiotherapy. We highlight practical aspects of delivering treatment and discuss toxicity and limitations, with particular reference to current practice in the United Kingdom.

## 1. Introduction

There is an ever-increasing demand for radiation techniques in the management of high-risk localised and locally advanced prostate cancer which allow dose escalation, whilst minimising the risks of acute and late severe toxicity. High-dose-rate (HDR) brachytherapy is ideally suited to achieving these goals for several reasons.

Here we discuss the history of HDR brachytherapy for high-risk prostate cancer with relevant radiobiological principles. We summarise important existing data and relate these to current practice in the United Kingdom.

## 2. Background

Prostate cancer is the commonest malignancy in men, and in the UK approximately 40,000 cases are diagnosed annually [1]. Incidence is increasing, partly due to the increasing use of the serum PSA assay in symptomatic and asymptomatic patients. There are many patients with prostate cancer who will not die from their disease, even without treatment in some cases. However, patients with more aggressive forms of the disease require an intensive approach to treatment to maintain a normal life expectancy.

Identifying these high-risk patients has long been a topic of debate and controversy. Improving knowledge of the biology of prostate cancer can help to guide patients in the clinic and is also of crucial importance to the design of therapeutic clinical trials: the development of increasingly aggressive treatments with the aim of cure has undoubtedly led to improved survival outcomes over time, but the risk of potentially serious short- and long-term iatrogenic side effects from "overtreating" patients at low risk should never be overlooked.

Surgical and radiotherapy series, including the use of pelvic lymphadenectomy [2, 3], have led to the identification of several factors associated with microscopic lymph node involvement and subsequent metastatic disease. These include serum PSA at presentation, Gleason score on biopsy, and clinical T (tumour) stage determined by clinical examination and, in later studies, by magnetic resonance imaging. In the UK risk is typically categorised using groupings based on those described by D'Amico et al. (Table 1) [2, 4].

In addition, an estimate of risk of lymph node involvement can be obtained using the Roach formula [5]:

$$\%\ \text{risk microscopic lymph node involvement} = \left(\frac{2}{3}\ \text{PSA}\right) + [(\text{Gleason score} - 6) \times 10]. \quad (1)$$

Table 1: Prostate cancer risk groups.

| Group | Criteria |
|---|---|
| Low risk | T1-T2a and PSA ≤ 10 ng/mL and Gleason score ≤ 6 |
| Intermediate risk | T2b or PSA > 10 ≤ 20 ng/mL or Gleason score 7 |
| High risk | ≥T2c or PSA > 20 ng/mL or Gleason score ≥ 8 |

## 3. Radiotherapy in High-Risk Prostate Cancer

Favourable long-term local control rates and overall survival are seen when high-risk patients are treated with primary radiotherapy in combination with the addition of androgen suppression, prior to and after radiotherapy [6–9]. This approach has therefore become a standard of care for patients with high-risk disease. The duration of long-term adjuvant androgen suppression after radiotherapy varies in published studies, but improvements in progression-free survival have been demonstrated where 2 or 3 years of androgen suppression are used, compared with durations of 6 months or less [8, 9].

Furthermore, although no direct comparison with radiotherapy has been made, surgical series have demonstrated that following radical prostatectomy a proportion of high-risk patients will later relapse following surgery, particularly where surgical margin positivity and/or extraprostatic disease are present [10–12]. Some of these patients may be cured with radiotherapy to the prostate bed at relapse, but at the expense of exposure to potential serious long-term toxicities from both surgery and external beam radiotherapy (EBRT). Prostatectomy for patients with high-risk disease is thus considered only in carefully selected patients [13].

The optimal radiotherapy treatment volumes for patients with high-risk disease remain unclear. There are data that support the practice of moderate-dose whole pelvic radiotherapy (WPRT) in this setting [14, 15], with a high-dose "boost" to the prostate itself. The relative contributions of WPRT and long-term androgen suppression are difficult to separate, however [15], and this approach is not without acute and late toxicity, particularly gastrointestinal complications. Studies to further evaluate the role of WPRT in high-risk patients are ongoing.

## 4. Background and Rationale for HDR Brachytherapy

*4.1. Dose Escalation. In vitro* and clinical studies show that there is correlation between prostate cancer survival endpoints and increasing radiation dose [16–18]. However, in practice this may be at the expense of increased toxicity, due to exposure of organs at risk where conventional conformal megavoltage photon external beam radiotherapy (EBRT) is employed.

For example, a 2002 randomised study of 305 patients treated at the MD Anderson Cancer Centre [18] demonstrated a reduction in clinical and biochemical failure rate at 6-year followup (64% versus 70%, $P = 0.003$) in patients who had received 78 Gy compared with those who had received 70 Gy external beam therapy to the prostate, across a range of risk groups. However, it was noted that where more than 25% of the rectum received a dose of 70 Gy or greater, the incidence of late rectal toxicity of grade 2 or greater increased to 30%. It is frequently not possible to limit the rectal dose using conventional EBRT techniques alone. Similar outcomes are seen in a number of other large phase III dose escalation studies using EBRT alone [16, 17].

*4.2. Radiobiological Principles.* Radiobiological research demonstrates that the probabilities of acute and late radiotherapy reactions vary between body tissues and tumours and between different radiotherapy dose-fractionation schedules. In particular, the likelihood of a *late* radiotherapy reaction or response is more dependent than *acute* reactions on the fraction size (dose per fraction) for a given total dose of radiation [19].

The *α/β ratio*, a means of expressing the sensitivity of a particular tissue to altered fraction size, is used to estimate the impact of a given schedule on tumour control and toxicity and enables comparisons to be made between schedules. Tissues and tumours with a low $\alpha/\beta$ ratio have a higher relative sensitivity to changes in fraction size than those with a high $\alpha/\beta$ ratio.

Fast-growing tumours have been demonstrated to have high $\alpha/\beta$ ratio (i.e., tumour responses are less dependent on fraction size; they may be more dependent on overall treatment time), whereas increasing evidence exists to support a *low* $\alpha/\beta$ ratio for prostate cancer, which may be as low as 1.5 Gy, in which case a hypofractionated approach (large doses in a small number of fractions) is favoured for optimal tumour control [20–23].

The EQD2 formula is frequently used to estimate the equivalent dose at 2 Gy per fraction for a given schedule:

$$\mathrm{EQD2} = D \times \frac{(d + \alpha/\beta)}{(2 + \alpha/\beta)}, \tag{2}$$

where $D$ is the total dose, $d$ dose per fraction, and the $\alpha/\beta$ ratio for a given tissue is used.

HDR brachytherapy lends itself to the delivery of a large radiation dose to the prostate in a small number of fractions (hypofractionation). For practical reasons (primarily the requirement to limit the number of invasive procedures and duration of patient immobility) it has in fact been necessary to deliver treatment in this way.

For example, a typical radical EBRT schedule for prostate cancer is given as 74 Gy, using a fraction size of 2 Gy. Table 2 illustrates the EQD2 estimations for the prostate for a variety of schedules used in published HDR brachytherapy series, assuming an $\alpha/\beta$ ratio of 1.5 Gy (see Table 2).

These doses are not achievable using EBRT alone, even with the use of more modern intensity-modulated techniques.

*4.3. Procedures.* At our centre HDR brachytherapy is delivered using the following technique.

Table 2: Estimated equivalent doses (2 Gy per fraction) for published HDR schedules using the EQD2 formula, assuming $\alpha/\beta$ for prostate cancer of 1.5 Gy [19].

| Author | Schedule | EQD2 prostate ($\alpha/\beta$ 1.5 Gy) |
|---|---|---|
| Galalae et al. [36] | 50 Gy WPRT, 40 Gy prostate EBRT, 2 fractions HDR (9 Gy per fraction) | 94 Gy |
| Åström et al. [30] | 50 Gy in 25 fractions EBRT, 2 fractions HDR (10 Gy per fraction) | 115.7 Gy |
| Martinez et al. [28] | 46 Gy in 23 fractions EBRT, 2 fractions HDR (11.5 Gy per fraction) | 131.4 Gy |
| Hoskin et al. [32] | 55 Gy in 20 fractions EBRT, 2 fractions HDR (8.5 Gy per fraction) | 115.4 Gy |

Under sterile conditions and with regional anaesthesia and following urethral catheterisation, up to 20 blind-ended needles are inserted into and adjacent to the prostate. To guide needle insertion, a transrectal ultrasound (TRUS) probe with stepping unit and template are used. This technique is similar to that originally described for the insertion of low-dose rate $^{125}$I seeds [24].

2 mm axial CT images of the pelvis are taken with the implant *in situ*. The prostate, rectum, and urethra are outlined using specialist planning software, and a planning target volume is created by adding a 3 mm margin around the prostate in all dimensions.

Source dwell positions and times are determined using specialist planning software, in order to deliver 15 Gy to the PTV in a single fraction, whilst doses to organs at risk are limited according to published guidelines [25]. Treatment is delivered using a single $^{192}$Ir source via an afterloading unit. Following treatment the needles are removed, and once haemostasis is achieved the urinary catheter is also removed.

There is no permanent implant with this technique; thus, no long-term radiation protection issues exist. A temporary implant also allows precise dosimetric calculations, so that the technique be used in combination with EBRT. This combination strategy is of particular relevance to high-risk patients, where it may be necessary to extend the treatment volume to include areas at high risk of microscopic spread (seminal vesicles and/or pelvic lymph nodes) to a moderate dose, whilst administering a high-dose boost to the prostate. It is not possible to treat these extended "prophylactic" volumes with brachytherapy alone.

*4.4. Clinical Data.* Although previously some centres had reported the use of iridium wire implants, the modern HDR brachytherapy prostate "boost" was first developed in the late 1980s in combination with external beam radiotherapy (EBRT) to the whole pelvis in intermediate- and high-risk patients. In an early study by the Michigan group [26], three fractions of HDR brachytherapy were given concurrently with EBRT in weeks 1, 2, and 3 of treatment. Brachytherapy was well tolerated, and 9 of the first 10 patients who underwent planned rebiopsy at 18 months after treatment were found to have no residual cancer.

With longer-term followup and comparison with a matched cohort [27], data emerged from this group to suggest superiority of HDR brachytherapy in this context, at least in terms of biochemical control, due to the much increased biologically effective dose delivered using the brachytherapy technique. An interim analysis confirmed improved biochemical control rates with two versus three fractions and with increased dose per fraction [28].

Data from this group were combined for analysis with those from two other institutions to establish the largest published series of over 600 patients [29]. A 73% 10-year biochemical control rate was observed across all treated groups, with disease-free survival of 49%, and encouraging results even in patients at high risk (69% biochemical control at 5 years). Although a variety of doses and schedules were employed between centres, encouragingly results were consistent.

Similarly, a Swedish group [30] reported 4-year follow-up data in 2005 on over 200 patients treated with EBRT to 50 Gy in 25 fractions with two fractions of HDR brachytherapy of 10 Gy each, in an interval midway through the EBRT. In the high-risk group (47 patients) overall 5-year biological no evidence of disease (bNED) was 61%.

Again, 10-year follow-up data from California (209 patients) [31] reported 69% bNED for the high-risk group.

The only prospective randomised controlled trial of EBRT alone versus EBRT with HDR brachytherapy boost, in 220 patients, reported significantly improved biochemical relapse-free survival in the brachytherapy group (5.1 years versus 4.3 years at median 30-month followup) with a reduction in acute rectal toxicity [32]. Although the dose-fractionation schedule in the EBRT arm of this study may now be considered suboptimal, these results do support previous data and the principles discussed and have supported further work evaluating dose escalation with HDR brachytherapy monotherapy in lower-risk patients [33]. It is recognised, however, that a direct comparison of HDR + EBRT and dose-escalated EBRT in intermediate- and high-risk patients has not been carried out.

A systematic review published in 2009 [34] compared results from studies evaluating high-dose (>75 Gy) EBRT, HDR brachytherapy with EBRT and low-dose rate seed brachytherapy with EBRT. Superior results, in terms of progression-free survival and overall survival, were seen for HDR brachytherapy and EBRT when compared with other techniques. This is likely to be due to the high doses achieved—it is noted that due to dose gradients within an HDR implant, there may be regions which receive far greater doses than those prescribed. The authors of this paper acknowledge that although every attempt has been made to account for confounding factors, marked variations between methods and definitions of survival endpoints in published studies mean that these results should be interpreted with

a degree of caution; nevertheless these data lend further support to the practice of HDR brachytherapy.

*4.5. Single Fraction HDR Brachytherapy.* The increasing body of evidence to support hypofractionation has led to the development of an "ultra-hypofractionated" single fraction HDR boost. This has obvious potential biological, practical, and cost-saving advantages, and any geometric uncertainty is virtually eliminated as there is no risk of interfraction variability.

The EQD2 to the prostate for a single fraction of 15 Gy, using a presumed $\alpha/\beta$ ratio of 1.5 Gy, is estimated at 70 Gy using the formula described. When combined with EBRT, an equivalent dose of up to 120 y in 2 Gy fractions is achievable.

The use of single fraction HDR brachytherapy in combination with EBRT in intermediate-risk patients has been reported [35]. At relatively short followup (median 1.14 years) biochemical control rates were excellent and observed toxicity acceptable; there was a notable lack of acute and late gastrointestinal toxicity. Genitourinary toxicity is far more common, partly due to difficulty avoiding high doses to the prostatic urethra; however, no severe late genitourinary toxicity has yet been observed in this cohort of 125 patients.

There has been much interest in this technique, which has also been adopted in a number of centres for the management of high-risk patients in combination with pelvic EBRT. Further work and followup are required, however, to evaluate the true long-term consequences of ultra-hypofractionation, and caution should be exercised particularly in patients with preexisting urinary symptoms (see Section 4.6).

*4.6. Toxicity.* Acutely, HDR brachytherapy commonly leads to an increase in urinary symptoms as measured by the IPSS score [32, 35–38]. However, this is generally short lived, and catheterisation is a rare event. Relatively high rates of late grade 3 urinary toxicity have been noted in patients who undergo postradiotherapy transurethral resection (TUR), and in those with large preexisting defects from previous TUR [31] HDR brachytherapy is relatively contraindicated, therefore, in patients with significant obstructive lower urinary tract symptoms prior to treatment [25]. Incontinence is an infrequent event.

Deterioration in potency is reported after HDR brachytherapy and EBRT in high-risk patients. However, there is much variation in method of assessment and the impact of androgen deprivation therapy is difficult to separate from the effects of radiotherapy. The rate of erectile dysfunction in this patient group is however high and increases with time (up to 76% at 7 years has been reported) [25].

There is no doubt that acute and late rectal toxicty rates are low following HDR brachytherapy. In the randomised trial [32], a significant reduction in acute rectal discharge was seen in the brachytherapy group, and in the single fraction study [35] only 6.5% of patients experienced acute grade 2 or greater gastrointestinal toxicity, with 10% grade 2 late toxicity. No severe late toxicity has been reported in this group, but again the short reported follow-up period is noted.

*4.7. HDR Brachytherapy in UK Practice.* HDR brachytherapy is an attractive treatment option for patients with high-risk disease, with the potential to increase dose and thus improve tumour control, as well as reducing toxicity and, from a practical viewpoint, reducing overall treatment time. It is becoming increasingly available and is currently practised in a number of UK centres. Its use is supported by the National Institute for Health and Clinical Excellence (NICE) [4] for use in combination with external beam radiotherapy in appropriately selected intermediate- and high-risk patients with nonmetastatic prostate cancer [4, 25].

The potential advantages of HDR brachytherapy over EBRT alone should be discussed with appropriate patients. It is important, however, that clinicians and patients alike are aware of the limitations of current data, when making decisions on the optimum treatment approach.

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*Research Article*

# The Role of Adjuvant Hormonal Treatment after Surgery for Localized High-Risk Prostate Cancer: Results of a Matched Multiinstitutional Analysis

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*Introduction*. To assess the role of adjuvant androgen deprivation therapy (ADT) in high-risk prostate cancer patients (PCa) after surgery. *Materials and Methods*. The analysis case matched 172 high-risk PCa patients with positive section margins or non-organ confined disease and negative lymph nodes to receive adjuvant ADT (group 1, $n = 86$) or no adjuvant ADT (group 2, $n = 86$). *Results*. Only 11.6% of the patients died, 2.3% PCa related. Estimated 5–10-year clinical progression-free survival was 96.9% (94.3%) for group 1 and 73.7% (67.0%) for group 2, respectively. Subgroup analysis identified men with T2/T3a tumors at low-risk and T3b margins positive disease at higher risk for progression. *Conclusion*. Patients with T2/T3a tumors are at low-risk for metastatic disease and cancer-related death and do not need adjuvant ADT. We identified men with T3b margin positive disease at highest risk for clinical progression. These patients benefit from immediate adjuvant ADT.

## 1. Introduction

Patients with high-risk localized prostate cancer (PCa) based on either PSA >20 ng/mL, Gleason score (GS) ≥8, or an advanced clinical stage have a risk of biochemical failure of up to 70% with surgery alone [1–5]. This has raised the question on the need of adjuvant treatments including androgen deprivation, radiation, and chemotherapy. Adjuvant androgen deprivation therapy (ADT) has shown significant improvement in disease-free survival for men with high-risk PCa treated with definitive radiation therapy and a survival benefit for men with GS 8–10 [6, 7]. For patients treated with radical prostatectomy (RP) the role of adjuvant ADT is still controversial. In a small prospective, randomized trial a survival benefit with adjuvant ADT in patients with lymph node positive disease was shown [8]. Two retrospective studies

have reported a survival advantage for immediate ADT in patients with locally advanced disease [9, 10]. For patients with pT3N0M0 PCa Thompson et al. recently reported improved metastasis-free and overall survival (OS) with adjuvant radiation therapy when compared to observation [11]. Current guidelines therefore recommend adjuvant radiation for these patients [12, 13]. However, the results of the ADT-alone control arm of the SWOG study S9921 reported on excellent 5-year progression-free (92.5%) and OS rates (95.9%) for men with high-risk PCa treated with RP and adjuvant ADT over a two-year period [14]. These excellent results were seen despite a minority of patients receiving adjuvant radiation and therefore suggest there might be a role for adjuvant ADT in men with pT3 disease and/or positive surgical margin.

The aim of our study was to analyze the role of adjuvant hormonal therapy in high-risk PCa patients with positive section margins or non-organ confined disease, but without nodal involvement, after radical prostatectomy in a matched European multicenter study cohort.

## 2. Materials and Methods

*2.1. Patient Population.* The study included 1413 patients with clinically localized high-risk PCa (PSA > 20 ng/mL, cT3-4, biopsy GS 8–10) and negative bone scan who had undergone RP at 7 tertiary referral centers between 1989 and 2005. Patients with positive section margins or non-organ confined disease and negative lymph nodes represented the study population. These patients were case matched in two groups receiving either adjuvant ADT within the first 3 months after RP (group 1) or no adjuvant ADT (group 2) (match criteria: age, clinical stage, biopsy and specimen Gleason score, pathological stage, and surgical margin status). Hormone deprivation was continuous and varied according to institutional preferences. Orchiectomy, LHRH-therapy, or maximal androgen deprivation with flutamide were performed. Neoadjuvant HT or adjuvant radiation therapy was considered as exclusion criteria. All patients were staged preoperatively with digital rectal examination (DRE), an abdominopelvic computed tomography (CT) scan, and bone scan. They underwent a wide radical prostatectomy with pelvic lymph node dissection. Our study group is not homogenous for the extent of lymphadenectomy and varied according to the institutional preferences, thus limiting our study in this point. Salvage therapy such as androgen deprivation (group 2 only) or radiotherapy was performed in individual patients at biochemical or clinical recurrence.

*2.2. Postoperative Evaluation and Endpoints.* Follow-up included a DRE and serum PSA analysis every 3 months for 2 years, every 6 months until 5 years after surgery, and annually thereafter. Imaging with US, CT scan, or bone scan was performed at the appearance of biochemical progression (BP), or manifest symptoms. BP was defined as PSA >0.2 ng/mL on 2 consecutive follow-up visits, clinical progression (CP) was either defined as local recurrence (confirmed by histology or imaging), or systemic recurrence (suspected by CT or bone scan). Prostate cancer-specific mortality (PCSM) was defined as the time from RP to death attributed to PCa or disease-related complications. Prostate cancer-specific survival (PCSS) was defined as the time from RP to PCSM. Overall survival (OS) was defined as the time from RP to death from any cause.

*2.3. Statistical Analysis.* Biochemical progression-free survival (BPFS), clinical progression-free survival (CPFS), overall survival (OS), and cancer-specific survival (PCSS) from the time of surgery were defined as endpoints for this retrospective analysis. Continuous variables were summarized as the mean and standard deviation. The Kaplan-Meier method was used to estimate the survivor function at various time points. Group comparisons were made using the log-rank test for survival endpoints. Univariate hazard ratios and their 95% confidence intervals (CI) were estimated using the Cox proportional hazards model. Prespecified clinical variables considered in the Cox model included the preoperative serum PSA, biopsy Gleason score, and clinical stage. Pathological stage, specimen Gleason score, surgical margin status, lymph node involvement, and adjuvant ADT were used as postoperative parameters. A $P$ value of $<0.05$ was considered statistically significant. Cox regression models were performed in order to identify subgroups of patients who either benefit from adjuvant ADT or never needed any ADT. Classification of subgroups was as follows: Gleason score <7/7/>7; positive and negative section margin pT2/T3/T4. Predefined endpoints were BP and CP. All analyses were performed with R statistical software (R, free software foundation). Multivariate analyses were insufficient to interpret since groups were too small.

## 3. Results

Out of 1413 patients 800 met the inclusion criteria. From these 86 were matched into each group. The homogeneity of both groups is shown in Table 1.

*3.1. Biochemical Recurrence-Free Survival.* At a median follow-up of 67 months 35.5% of the patients developed BP. BP was less frequent in group 1 when compared to group 2 (Table 2). The univariate Cox regression analyses are presented in Table 3.

*3.2. Clinical Progression-Free Survival.* Of the 86 patients in group 1 only 5 (5.8%) experienced CP during follow-up. On the contrary—although follow-up for clinical recurrence was available only for 46 patients in group 2—CP was seen in 12 of these 46 patients available for analysis (26.1%). Estimated 5- and 10-year CPFS 96.9% and 94.3% for group 1 and 73.7% and 67.0% for group 2, respectively ($P < 0.01$) (Table 2). None of the men with T2 tumors developed CP, and the risk for T3a disease was fairly low (2/28 in group 1 versus 4/29 in group 2, $P = 1.0$). But all patients who developed CP had positive section margins. The risk was highest in men with seminal vesical invasion (T3b) and univariate cox regression analysis comparing both groups showed that

Table 1: Preoperative and postoperative characteristics of the 172 matched patients.

| Characteristic | Group 1<br>Adjuvant ADT | Group 2<br>No adjuvant ADT |
|---|---|---|
| Patients number | 86 | 86 |
| Median age (years) | 66.2 | 66.6 |
| Median Follow-up (months) | 69 | 66 |
| Mean PSA, ng/mL (range) | 31.5 (3–119) | 28.4 (2.78–159) |
| Clinical stage, 1997 TNM, (number (%)) | | |
| ≤cT2 | 36 (41.8%) | 48 (55.8%) |
| cT3 | 49 (57.0% ) | 37 (43.0%) |
| cT4 | 1 (1.2 %) | 1 (1.2%) |
| Biopsy Gleason score (number (%)) | | |
| ≤6 | 36 (41.8%) | 44 (51.2%) |
| 7 | 39 (45.3%) | 32 (37.2%) |
| ≥8 | 11 (12.9%) | 10 (11.6%) |
| Pathol. stage, 1997 TNM (number (%)) | | |
| pT2 | 4 (4.7%) | 9 (10.5%) |
| pT3a | 28 (32.5%) | 29 (33.7%) |
| pT3b | 50 (58.1%) | 45 (52.3%) |
| pT4 | 4 (4.7%) | 3 (3.5%) |
| Pathol. Gleason score (number (%)) | | |
| ≤6 | 34 (39.5%) | 34 (39.5%) |
| 7 | 39 (45.4%) | 39 (45.4%) |
| ≥8 | 13 (15.1%) | 13 (15.1%) |
| Surgical margins (number (%)) | | |
| Positive | 62 (72.1%) | 66 (76.7%) |
| Negative | 24 (27.9%) | 20 (23.3%) |
| Salvage therapy | | |
| ADT | 0 (0.0%) | 25 (29.1%) |
| Radiotherapy | 3 (3.5%) | 9 (10.5%) |

PSA: prostate-specific antigen; ADT: androgen deprivation therapy.

Table 2: Freedom from biochemical progression free-survival (BPFS), clinical progression-free (CPFS), cancer-specific (CSS), and overall survival (OS).

| Projected survival | Group 1 ADT ($n = 86$) | | Group 2 no ADT ($n = 86$) | | $P$ value |
|---|---|---|---|---|---|
| | 5 years | 10 years | 5 years | 10 years | |
| BPFS | 87.7% | 76.3% | 37.1% | 30.6% | <0.001 |
| CPFS | 96.9% | 94.3% | 73.7% | 67.0% | 0.003 |
| CSS | 100% | 100% | 100% | 91.0% | 0.9 |
| OS | 94.4% | 83.8% | 97.1% | 76.4% | 0.6 |

Table 3: Univariable cox regression models for comparing groups 1 and 2; endpoint: biochemical recurrence and clinical progression. (For clinical progression follow-up data were available for 132 patients).

| | Biochemical progression | | Clinical progression | |
|---|---|---|---|---|
| | HR (95% CI) | $P$ value | HR (95% CI) | $P$ value |
| Whole sample | 0.15 (0.08–0.29) | <0.001 | 0.21 (0.08–0.6) | 0.003 |
| Low Gleason <7 | 0.16 (0.08–0.31) | <0.001 | 0.25 (0.08–0.8) | 0.02 |
| High Gleason ≥7 | 0.11 (0.01–0.86) | 0.04 | 0.18 (0.02–1.6) | n.s. |
| R0 | 0.13 (0.03–0.48) | 0.002 | 1.15 (0.1–13.4) | n.s. |
| R1 | 0.16 (0.75–0.32) | <0.001 | 0.15 (0.04–0.53) | <0.01 |
| pT3a | n.s. | n.s. | n.s. | n.s. |
| pT3b | 0.15 (0.08–0.29) | <0.001 | 0.26 (0.09–0.75) | 0.013 |
| pT4 | 0.22 (0.02–2.1) | n.s. | n.s. | n.s. |

tumor stage, surgical margin status, and Gleason score were predictors for CP (Table 3). The numbers were too small for multivariate cox regression analysis.

*3.3. Cancer-Specific Survival and Overall Survival .* Survival for the entire cohort was excellent. There have been 20 deaths (11.6%) including only 4 PCa-related deaths (2.3%). Although there was no statistically significant difference for OS and PCSS between both groups none of the patients in group 1 died PCa-related while 4 in group 2 died on their prostate cancer. The estimated 10-year. OS and PCSS was 83.8% and 100% for group 1 and 76.4% and 91.0% for group 2, respectively (Table 2).

## 4. Discussion

There is increasing evidence that surgery provides a reasonable treatment option for selected men with high-risk prostate cancer [1, 5, 15, 16]. The recently reported results of the control arm of the SWOG-study S9921 showed that the combination of surgery and combined adjuvant ADT is associated with favorable disease-free and overall survival of greater than 92% at 5 years of follow-up [14]. Our study results corroborate these better than expected survival rates even for a high-risk cohort with positive section margins or non-organ confined disease and negative lymph nodes (8-year PCSS 97.5% and OS 92.7%). The results reported here and in the S9921-trial together with the improved outcomes for the combination of radiation and ADT in men with high-risk prostate cancer support the use of a multimodal treatment including adjuvant ADT [7, 8, 17]. However, the survival rates reported in these trials reach up to 90% for PCSS and 76% for OS, indicating that what we currently define as "high-risk" disease group indeed is a heterogeneous cohort with better than expected outcomes. These limitations in risk assessment are also visible in the adjuvant radiation therapy (RT) trials. Although some differences exist among the inclusion criteria, these studies showed a benefit for immediate adjuvant radiation in terms of biochemical progression (hazard ratio 0.47, 95% CI: 0.4–0.56, $P < 0.0001$) [17]. But only the SWOG-study could show a significant improvement in metastasis-free and OS of 1.8 and 1.9 years, respectively [11]. Overtreatment is obvious from these RT trials: the number needed to treat was 12.2 to prevent metastasis in one patient at 12.6 years of follow-up and the number needed to treat was 9.1 to prevent one death at the same time. Therefore, Colette et al. tried to substratify the patients from EORTC-trial 22911 and identified men with positive section margins to be at higher risk for biochemical progression (relative risk reduction of 62% for irradiated men, HR 0.38) [18].

The excellent outcomes observed in men receiving adjuvant ADT raise two questions. (1) Overtreatment; the results of the control arm of the S9921-trial show better than expected survival rates with adjuvant ADT over a two-year period [14]. These excellent results raise the question whether adjuvant ADT was necessary in all patients after surgery. ADT is related to a wide variety of metabolic and cardiovascular effects that impact morbidity and mortality of PCa patients [19]. Treatment deescalation therefore is an important step forward in treating men with PCa. Our matched analysis showed that 43% of the patients treated by RP alone never experienced BP during follow-up and the estimated 10-year biochemical progression-free survival for this group was 30.6%. However, PSA is limited as an outcome parameter and not all patients with biochemical recurrence will develop metastasis and finally die on their PCa thus limiting this information in patients counseling [20, 21]. Analysis therefore should be focused on clinical progression and survival. Although our data for group 2 are limited in terms of clinical recurrence—follow-up information for this outcome measure were available only for 46/86 men in this group—the risk for CP was significantly lower for group 1 when compared to group 2 (5.7% versus 26.1%). Men with T2 and T3a tumors (irrespective to the surgical margin status) had a very low risk of CP and PCSM and therefore adjuvant ADT can be avoided in these patients. (2) The excellent outcomes make compelling argument for a better definition of high-risk patients for future trials. We identified tumor stage, surgical margin status, and Gleason score as predictors for CP. Men with T3b margin positive disease are at increased risk for CP and benefit from adjuvant ADT with a hazard ratio of 0.25 when comparing group 1 and 2. EAU guidelines state two options that can be offered to patients with pT3b tumors and positive margins: either an immediate radiotherapy to the surgical bed, upon recovery of urinary function, or monitoring followed by salvage radiotherapy at PSA rising, not exceeding 0.5 ng/mL (level of evidence 1 and 3) [12]. However, this trial was conducted to assess the role of adjuvant ADT in high-risk PCa patients after surgery. Since this study lacks a radiotherapy arm, comparison to other adjuvant therapy regimens cannot be drawn. Side effects, costs, and benefits have to be considered when deciding on adjuvant therapy. In our study survival rates were excellent—only 11.6% of the patients died overall and 2.3% tumor related. Although not statistically significant some differences in the outcome between both treatment groups have to be mentioned. None of the patients in group 1 died tumor related versus 4 in group 2. All of these 4 men had positive surgical margins and 3/4 T3b tumors, thus suggesting that these patients might benefit from immediate adjuvant ADT. In general, the risk of death is rather low even for the group of T3b patients. Further subanalyses are necessary to identify those men at highest risk for CP and PCSM. It is important to mention that all patients in the adjuvant ADT group received continuous ADT. It is therefore not possible to address the question whether this approach is superior to shorter-term adjuvant ADT or PSA-triggered ADT. In a retrospective study Siddiqui et al. reported on the outcome of a contemporary RP cohort of 6401 men and compared the outcome of immediate-versus deferred PSA-triggered ADT and found no differences in CSS [22].

We recognize that our study is not without limitations. Its retrospective nature may have caused a selection bias towards patients who, although considered high risk, were still deemed suitable for surgery. Variations in the extent of lymphadenectomy and in pathology review as well as the use of salvage treatments might have influenced our results.

The study design and the low number of events (clinical recurrence, and PCSM) limit the power of the analysis.

Despite these limitations, the results of this matched multicenter study on RP and adjuvant ADT provide useful information for clinical decision making for men with high-risk prostate cancer and adverse histopathological parameters.

## 5. Conclusion

Our results indicate excellent outcomes for high-risk prostate cancer with positive section margins or non-organ confined disease but negative lymph nodes after surgery. Patients with T2/T3a tumors are at low risk for metastatic disease and cancer-related death even in case of positive section margins—adjuvant ADT therefore can be avoided in these patients. Pathological stage and section margin status allows us to identify men with T3b surgical margin positive disease at highest risk for clinical progression. These patients benefit from immediate adjuvant ADT. However, such risk stratification is limited and far away from personalized therapy. Research energy should be focused on the identification and validation of new molecular markers to identify lethal disease. We recently described a new biomarker to predict clinical recurrence in high-risk PCa patients [23].

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*Review Article*

# Radical Prostatectomy and Intraoperative Radiation Therapy in High-Risk Prostate Cancer

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Intraoperative electron beam radiotherapy (IOERT) for prostate cancer (PC) is a radiotherapeutic technique, giving high doses of radiation during radical prostatectomy (RP). This paper presents the published treatment approaches for intraoperative radiotherapy analyzing functional outcome, morbidity, and oncological outcome in patients with clinical intermediate-high-risk prostate cancer. A systematic review of the literature was performed, searching PubMed and Web of Science. A "free text" protocol using the term intraoperative radiotherapy and prostate cancer was applied. Ten records were retrieved and analyzed including more than 150 prostate cancer patients treated with IOERT. IOERT represents a feasible technique with acceptable surgical time and minimal toxicity. A greater number of cases and longer follow-up time are needed in order to assess the long-term side effects and oncological outcome.

## 1. Introduction

The optimal treatment of locally advanced PC is still unclear [1]. The use of radical prostatectomy (RP) alone is controversial, and external beam radiation (EBRT) associated with hormonal therapy (HT) has been the traditional treatment modality for this stage of disease [2]. However, even with the use of multimodal approaches, only a 37–62% and 44% disease-free survival at 5 and 10 years can be obtained [3–7] and side effects of these treatments are not limited [2].

With the aim to improve the clinical outcomes of locally advanced PC, various radiotherapeutic approaches have been implemented. IOERT is being investigated as a technique to deliver a high dose of radiation to a locally advanced tumor protecting adjacent normal tissues at the time of surgery. This new technique has been used for treatment of several tumours as a boost or sole radiation treatment before or after tumour resection with the aim to improve local tumour control. Different approaches and different accelerators have been used, as reported in technical and dose-finding studies.

IOERT for PC was first proposed in Japan more than twenty years ago, either as a single treatment [8, 9] or combined with pelvic lymphadenectomy (PLND) or EBRT to pelvic lymph nodes [10, 11]. Recently, three Italian centers have reported series of intermediate and high-risk PC patients treated with IOERT combined with RP and PLND [12–14]. The potential advantage of IOERT is to allow optimal targeting and identification of the prostate and surrounding structures. Recent radiobiological studies suggest that the use of a single high fraction of radiation may increase the efficacy of the treatment leading to higher tumor cell killing [15].

The aim of this paper is to describe the different technical approaches of IOERT and the available results in terms of clinical outcome for locally advanced PC.

## 2. Material and Methods

A literature search was performed using PubMed and Web of Science from 1975 to 2011. The keywords IOERT and

Table 1: Treatment modality and outcomes of selected series of IORT in prostate cancer.

| | pts | Treatment modality | Local control | Overall survival (5 years) | Morbidity, toxicity, and surgical complications |
|---|---|---|---|---|---|
| Takahashi et al. [9] | 9 | IORT(20–25 Gy) + PNLD + EBRT(50 Gy) ± HT—without RP | 100% 5y | — | No severe toxicity |
| | 5 | IORT(30–35 Gy) + PNLD ± HT—without RP | 80% 5y | | No severe toxicity |
| Abe et al. [17] | 21 | IORT (28–35 Gy) single dose + PNLD—without RP<br>IORT(20–25 Gy) + EBRT(50 Gy) ± HT | 81% 5y | 72% | 100% hematuria |
| Kojima et al. [10] | 30 | IORT(12–20 Gy) + PRP/RRP ± PNLD + EBRT ± HT | — | 43% | — |
| Higashi et al. [11] | 35 | PNLD + IORT(25–30 Gy) + EBRT(30 Gy) ± HT—without RP | — | 92% (stage B)<br>87% (stage C) | No severe toxicity |
| Saracino et al. [12] | 34 | IORT(16–22 Gy) + RRP ± PNLD + EBRT ± HT | 91% | — | No severe toxicity |
| Rocco et al. [19] | 33 | RRP + PNLD + IORT(12 Gy) + EBRT ± HT | — | — | 1 lymphocele<br>3 anastomotic stricture |
| Krengli et al. [14, 20] | 38 | RRP + PNLD + IORT(9–12 Gy) + EBRT ± HT | — | — | 11% G2 GE toxicity<br>4% G2 GU toxicity<br>5 lymphocele<br>2 pelvic hematoma |

RP = radical prostatectomy, PRP = perineal radical prostatectomy, RRP = retropubic radical prostatectomy, PLND = pelvic lymphadenectomy, EBRT = external-beam radiation, HT = hormonal therapy, GE = gastro-enteric, GU = genito-urinary.

PC were used. A free-text strategy was applied without limitations. We retrieved 11 references dealing with IOERT and PC (Table 1). Only phase I-II studies are available. No randomized clinical trials (RCTs), systematic reviews of cohort studies, and low-quality RCTs are reported. The aim was not to produce a meta-analysis but to critically evaluate and discuss the use of IOERT in the treatment of PC.

## 3. Result

The first series of IOERT for PC was reported by the Kyoto University and Saitama Cancer Center in Japan. The authors initially carried out IOERT as single treatment or in combination with PLND or EBRT to pelvic lymph nodes [9–11, 16, 17]. Perineal approach without RP using electron energy from 10 to 14 Mev has been performed in 14 patients by Takahashi et al. [9]. Five patients treated by IOERT alone received single doses of 2800 to 3500 cGy. Two patients treated with 2800 and 3000 cGy, respectively, had local recurrence. A single dose of 2000 or 2500 cGy was delivered intraoperatively to 9 patients as a boost dose in conjunction with external irradiation of 5000 cGy for the treatment of pelvic lymph nodes. All these patients achieved local control. No patients in the overall series developed serious bladder, urethral, or rectal complications. An update from the same center reported a local control and 5-year survival rates of 81% and 72%, respectively, with 2% late toxicity consisting of chronic cystitis and urethral stricture [17].

The experience of the Saitama Cancer Center began with the perineal approach and switched to the retropubic approach after the first 10 cases, due to the potential risk of rectal damage, impossible PNLD, and patient discomfort [10, 11]. Radiation therapy included 25–30 Gy of IOERT on the prostate and 30 Gy of external beam radiotherapy to the small pelvic region. Most patients received additional androgen ablation treatment. The authors reported 92% and 87% overall survival rates in 35 patients with stage B and stage C disease, respectively, without severe side effects.

More recently, Italian authors reported phase I-II studies with a relatively higher number of patients compared with the Japanese series [12–14, 18, 19].

A different treatment approach was adopted by three Italian centers. In Saracino's series, 34 patients with localized PC with only one high-risk factor (Gleason score ≥ 7, clinical stage ≥ T2c, or prostate-specific antigen of 11–20 ng/mL) and without clinical evidence of lymph node metastases were treated with RP and IOERT on the tumor bed. Dose levels of 16, 18, and 20 Gy were selected [12]. The IOERT procedure was performed after prostate removal and at the end of bladder-urethral anastomosis. Negative frozen section of bilateral obturator nodes was mandatory. In vivo dosimetry was performed by MOSFET dosimeters inserted in rectal and urethral catheters in order to obtain a reliable dosimetry at the level of the bladder-urethral anastomosis [18].

After a median follow-up of 41 months, the authors reported a local control rate of 91% with biochemical-failure-free survival at 3 years of 77%. They did not observe any relevant early or late toxicity. In this series, unfavorable prognostic factors were stage >T3, PSA > 10 ng/mL at univariate analysis, and surgical positive margins at both univariate and multivariate analyses. Of note, postsurgical T2 stage was detected in 53% of cases [12].

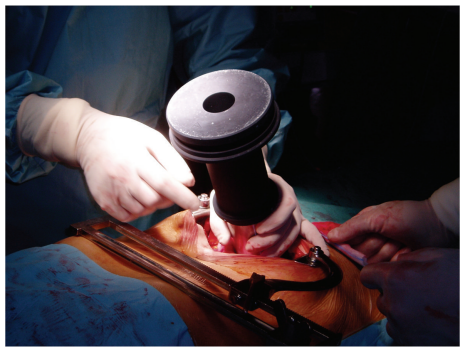

Figure 1: The appropriate collimator is placed and beam energy is chosen in order to include the prostate gland and the surrounding soft tissues with a suitable margin of 0.5–1 cm.

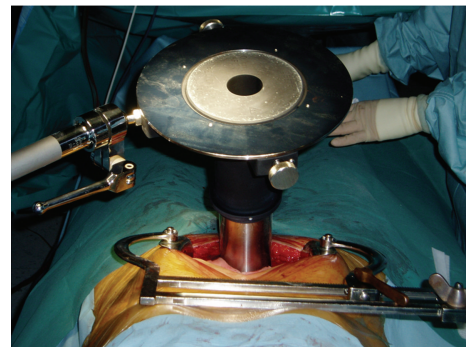

Figure 2: The collimator is fixed to the operating table.

Figure 3: Dedicated linear accelerator (Mobetron, Intraop, Sunnyvale, CA) installed in the operating room.

Orecchia et al. and Krengli et al. reported on 11 and 38 patients, respectively, treated in a similar fashion as in Saracino's study but before prostate removal. In these series, IOERT was not used as a single radiation treatment modality but as an anticipated boost followed by postoperative EBRT according to the pathological findings. A dose of 10–12 Gy was prescribed to the 90% isodose using 9–12 MeV IOERT [13, 14]. In these two series, surgery is performed with a median abdominal incision to approach the retropubic space. The pelvic fascia is prepared and the anterior face of the prostate exposed. Puboprostatic ligaments are sectioned and the deep dorsal vein plexus controlled. The apex of the prostate and the endopelvic urethra are visualized. A stitch is placed as a marker of the bladder neck. The anterior-posterior prostate diameter and the distance from prostate surface to the anterior rectal wall are measured by intraoperative ultrasound. Based on clinical and ultrasound parameters, the appropriate collimator and beam energy are chosen in order to include the prostate gland and the surrounding soft tissues with a suitable margin of 0.5–1 cm Figures 1 and 2. Orecchia et al. administered IORT using a Liac (Info and Tech, Rome, Italy) mobile linear accelerator, while Krengli et al. used a dedicated linear accelerator (Mobetron, Intraop, Sunnyvale, CA) installed in the operating room, delivering electron beams of 9 to 12 MeV for a total dose of 12 Gy (Figure 3). Rectal dose was measured "in vivo" by radio-chromic films placed on the surface of a rectal probe. Three-dimensional conformal RT was delivered 3 months after surgery using 4 to 6 customized beams for a total dose of 46–50 Gy in 25 fractions (2 Gy/fraction) in case of extracapsular extension and/or positive surgical margins at pathology. Adjuvant HT was recommended for 2 years in presence of pT3b-T4 disease or positive lymph nodes (LN+). In case of biochemical failure permanent HT was given [14].

In 2009 Rocco et al. reported an update of their series, comparing in a matched-pair analysis 33 high-risk patients treated by IOERT with a historical group of 100 patients who underwent RP and adjuvant RT and HT [19]. After a median follow-up of 16 months, only 1 of 33 patients experienced biochemical failure. Surgical outcome was equivalent in the two groups, whereas the urinary continence rate was lightly worse in the IOERT group. However, the continence improved similarly over time in both patient groups. Postsurgical T2 stage was detected in 36% of cases, while most cases were classified as pT3 [19].

The series by Krengli et al. was updated in terms of patient number and clinical outcome in 2010 [20]. After a median follow-up of 24 months, all patients were alive and 18% experienced biochemical failure with median time to progression of 27 months (range 6–44). Toxicity and surgical complication rates were low. Complications mainly consisted of lymphoceles (16%) and pelvic hematomas (6%). Eighty-four percent of patients were fully continent, and no grade 3-4 late toxicity was observed. Postsurgical T2 stage was detected in 37% of cases, and most cases were pT3.

## 4. Discussion

Optimal treatment strategy for locally advanced PC remains unknown. Local control after RP depends on Gleason score, preoperative PSA level, pathological stage, and margins status [21].

Multimodal approach which includes adjuvant HT or RT after RP clearly improves the outcomes in men with locally advanced PC [22, 23]. The rationale of IOERT in locally advanced PC is based on the unsatisfactory results obtained by other treatment modalities [24]. Using IOERT, it is possible to irradiate the whole surgical bed, including the tissues surrounding the prostate with a limited dose to the rectum.

IOERT dose of 12 Gy at the 90% isodose compared to doses delivered with conventional EBRT fractionation is similar to the normalized dose of 56.2 Gy with an alpha/beta ratio of 1.5 Gy. The mean dose delivered to the prostate bed of 8.7 Gy reported by Orecchia et al. [13] corresponds to 25.4 Gy with a conventionally EBRT fractionated regimen. Such dose combined with the further 45–50 Gy delivered postoperatively would reach a total dose of 70–75 Gy.

In the Japanese series, patients were treated without RP, with a potential risk of local recurrence.

The techniques used in the Italian studies are different. Orecchia et al. and Krengli et al. reported complete prostate removal after IOERT, while Saracino et al. carried out IOERT after retropubic RP. The first approach aims to optimize the irradiated volume including prostate and surrounding tissues possibly infiltrated by tumor cells. It allows an optimal placement of the most appropriate collimator that can vary in size and bevel angle [14]. Ultrasound measurements of prostate diameter and distance from the rectal wall can help in the choice of the most appropriate beam energy and allows addition of bolus material to modify and optimize the distribution in depth of the radiation dose when needed. Using this technique, the dose to the rectum can be limited because of the interposition of prostate tissue. Finally, this approach can potentially achieve a better irradiation of the prostatic apex, which is frequently a site of recurrence. An important point to underline for any technical approach is the need of precise documentation in terms of quality assurance, such as "in vivo" rectal dosimetry and possibly urethral dosimetry.

Different from the Japanese old experience that delivered a relatively high single dose of 28–35 Gy or of 20–25 Gy when combined with EBRT to the target, Saracino et al. used a single dose up to 22 Gy in intermediate-risk patients, while the other Italian authors used a more conservative approach delivering only part of the dose by IOERT (12 Gy) and adding EBRT in patients with positive margins or extracapsular disease.

A potential critical aspect of this approach is the time interval between IOERT and EBRT, that is, about 2-3 months. The rationale of this delay is to allow an adequate recovery of tissues from surgical trauma and to minimize the risk of persistent urinary incontinence.

RP is performed according to the recommended technique for locally advanced PC [25]. The additional time required for IOERT is short, on average 30 minutes [12–14, 19].

In the Italian IOERT studies there are no significant differences in terms of surgical complications, early toxicity, 1-year continence rate, and late side effects [12–14, 19]. No major surgical complications were described by all authors. Rocco et al. reported higher blood loss and need of transfusion for IOERT patients compared to those treated by conventional RP. However, this difference was not statistically significant (42% versus 30%) [19].

IOERT gastrointestinal and genitourinary toxicities are always low and similar to those of EBRT [26, 27]. In Rocco's paper, a comparable toxicity between IOERT + EBRT and EBRT was also reported [19].

Rectal dosimetry showed a mean dose delivered to the anterior rectal wall of 3.5 Gy with a range of 0.44–7.99 [14, 20]. A relevant dose reduction was constantly observed at the level of the posterior rectal wall showing that the rectum was in the steep component of the in-depth dose-distribution curve.

Several questions still remain unsolved. IOERT is part of multidisciplinary approaches for high-risk, locally advanced PC. Therefore, it is difficult to discriminate its contribution to the oncological outcomes. Furthermore, the published series are small and with short follow-up and the optimal IOERT technique is still unclear (IOERT before or after prostate removal, dose of radiation). Current clinical staging is not optimal, and a proportion of patients are at risk of overtreatment when IOERT is delivered (about 1/3 of the patients in the literature series had negative surgical margins and pT2 disease).

## 5. Conclusion

IOERT is safe and feasible with a low complication rate after short-intermediate follow-up. Combined RP and IOERT are potentially an effective first step in the multimodality approach for the treatment of high-risk PC. Finally, comparative trials are needed to allow a statistically powerful comparison of IOERT outcomes with those of gold standard treatments for high-risk PC. Until long-term safety and oncological results of IOERT are not available, this technique should be considered an experimental option in the treatment of high-risk PC.

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*Research Article*

# Complications and Functional Results of Surgery for Locally Advanced Prostate Cancer

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The role of surgery in clinical stage T3 prostate cancer (cT3 PCa) is still subject to debate. We reviewed the records of 139 consecutive patients who underwent a radical prostatectomy (RP) for cT3 PCa with a mean follow-up of 8 years. All data related to surgical and perioperative complications were collected. Continence and erectile function were assessed at 12 months postoperatively and long-term oncologic outcomes were analyzed. Rectal injury and injury of the obturator nerve occurred both in 0.7% of cases. No serious in-hospital complications were noted and no reintervention was needed. Lymphatic leakage was noted in 2.2% of patients and 1.4% experienced prolonged drainage of urine. In 7.2%, wound-related problems occurred. Anastomotic stricture occurred in 2.9%. These complication rates were not different compared to surgical series of RP in localized PCa. At 12 months, complete continence was 87.8% and erectile function had fully recovered in 6% and 10% of patients who underwent a non-nerve sparing or unilateral nerve-sparing procedure, respectively. 10-year estimated biochemical PFS, clinical PFS, CSS and OS were 51.8%, 85.6%, 94.6% and 85.9%, respectively. In cT3 PCa, RP is technically feasible with morbidity comparable to RP in clinically localized PCa. Long-term oncologic control was excellent.

## 1. Introduction

Locally advanced prostate cancer (PCa) is defined as cancer that has extended clinically beyond the prostatic capsule with invasion of the pericapsular tissue, the sphincter muscle, bladder neck, or seminal vesicles, but without lymph node involvement or distant metastases [1]. Locally advanced PCa is referred to as clinical stage T3-4 N0 M0 disease. T-staging is mainly based on the findings of digital rectal examination, while transrectal ultrasound, PSA level, PSA density, and the extent of cancer in prostate biopsies may provide additional information [2]. In a recent population-based Swedish study, 18.6% of prostate cancers presented as locally advanced, nonmetastatic PCa [3]. In another recent paper, based upon data from the SEER (Surveillance, Epidemiology, and End Results) database, between 11.6% and 15.3% of the patients presented with cT3 N0 M0 PCa, while 8% to 10.9% presented with T4 and/or N1 and/or M1 PCa [4]. These data from Europe and the US provide an estimation of the incidence of cT3-4 PCa, which is thought to be between 15 and 25%.

The optimal treatment of cT3 PCa has been subject to intense debate during recent years. According to the guidelines of the European Association of Urology (EAU), watchful waiting, radiation therapy (RT), Radical prostatectomy (RP), hormonal therapy (HT), and various combinations are valuable options to consider, depending on the general health status of the patient and the local extent of the tumour [5].

Many experts consider an RP for cT3 PCa a valid treatment option with excellent oncological outcome, but it is felt to be a burdensome procedure even for a skilled surgeon and feasibility has been questioned in the past.

In order to better define the place of surgery in cT3 PCa, we have conducted a retrospective study in 139 patients who underwent an RP for cT3 PCa. The patient files were critically reviewed and all data related to surgical and peri-operative complications were carefully collected. All data were compared to major contemporary series of RP in clinically localised disease. Additionally, functional results with respect to erectile function and continence were collected at 12 months postoperatively and long-term oncologic outcomes were assessed.

## 2. Material and Methods

From January 1997 to December 2003 we performed an RP with bilateral pelvic lymphadenectomy in 139 patients with cT3 PCa. Ultrasound guided prostate biopsies showed a median Gleason score of 7 (range 2–10). Prostate biopsy was performed in accordance with the random systematic octant biopsy technique: lateral systematic sextant biopsies with additional bilateral transition zone biopsies [6]. Additional biopsies were directed to the sites of abnormal digital rectal examination and abnormal transrectal ultrasound findings. Local staging was routinely performed by digital rectal examination and transrectal ultrasound. In 16 patients, endorectal coil magnetic resonance imaging was included to refine the local staging. Lymph node status was examined through a contrast-enhanced CT scan of the pelvis ($n = 122$) or an MRI scan ($n = 4$). Distant metastases were excluded by a bone scan ($n = 123$). In patients with PSA <10 ng/mL and a biopsy Gleason score <7, N and M staging was not performed, as the risk for nodal involvement in this group is estimated to be very low (≤4%) [7]. 125 patients (89.9%) were staged cT3a N0 M0 and 14 (10.1%) cT3b N0 M0 (Table 1).

As described earlier, our surgical technique focuses on clean apical dissection, neurovascular bundle resection at least at the tumour bearing site, complete resection of the seminal vesicles, and in some cases resection of the bladder neck [8]. In 129 patients (92.8%), a bilateral non-nerve-sparing RP was performed. In only 10 patients (7.2%), a unilateral nerve-sparing procedure was possible. In 10 patients (7.2%) a lymphadenectomy was not performed because of previous pelvic surgery or a low PSA level (<10 ng/mL) associated with a biopsy Gleason score <7.

In the peri-operative period, low molecular weight heparin and compression stockings were administered as thromboembolic prophylaxis. Postoperative pain was managed for 2 days by epidural patient-controlled anaesthesia. Oral ingestion and early mobilisation was encouraged from the first postoperative day. Patients were discharged after removal of all suction drains (as soon as drainage was fewer than 15 mL per 24 h), as soon as they were on a normal diet and were fully ambulatory and pain or discomfort was manageable by oral analgesia. The urethral catheter was left in situ at discharge and was removed during a one-night hospital stay at a mean of 12 days postoperatively. Since our group has shown that pelvic floor muscle exercises shorten the duration of incontinence and improve continence rates after an RP, physiotherapy was started at catheter removal [9]. Patients who remained incontinent at 1 year were offered the possibility of an artificial urethral sphincter implant.

At 6 to 8 weeks postoperatively, patients were reassessed for the first time and serum PSA was measured. For the first postoperative year, patients were seen at 3-month intervals. For the second and third years, patients were reevaluated every 4 months and 6 months thereafter.

Patients who underwent a unilateral nerve-sparing procedure were offered treatment with 5-phosphodiesterase-inhibitors, or intracavernous prostaglandin E2 injections if the obtained effect was insufficient. Patients who underwent a non-nerve-sparing operation were offered treatment with intracavernous injections.

Table 1: Patient characteristics.

| | |
|---|---|
| Number of patients | 139 |
| Age (years), mean (±SD) | 61,8 (±7,0) |
| cT3a | 89,9% ($n = 125$) |
| cT3b | 10,1% ($n = 14$) |
| Biopsy Gleason score, median (range) | 7 (2–10) |
| PSA (ng/mL), mean (range) | 13,73 (3,1–97,0) |
| Previous surgery | 14,4% ($n = 20$) |
| Neo-Adjuvant Androgen Deprivation Therapy | 8,6% ($n = 12$) |
| Non-nerve-sparing procedure | 92,8% ($n = 129$) |
| Unilateral nerve sparing procedure | 7,2% ($n = 10$) |
| Lymphadenectomy not performed | 7,2% ($n = 10$) |
| Hospital stay (days), median (range) | 12 (5–27) |
| pT2 | 31,1% ($n = 42$) |
| pT3a | 51,1% ($n = 69$) |
| pT3b | 16,3% ($n = 22$) |
| pT4 | 1,5% ($n = 2$) |
| PSA persistence | 10,1% ($n = 14$) |
| Pathological Gleason score, median (range) | 7 (4–9) |
| Pathological node positive | 10,1% ($n = 14$) |
| Surgical margin positive | 13,7% ($n = 19$) |
| Adj radiation therapy within 1 year | 7,2% ($n = 10$) |
| Adj endocrine therapy within 1 year | 13,7% ($n = 19$) |

Further treatment strategy was based upon final histopathology and PSA evolution. In case of positive surgical margins, patients were randomised according to the EORTC 22911 protocol to receive adjuvant pelvic irradiation or not [10]. In case of positive lymph nodes, early endocrine treatment was initiated. Invasion of the seminal vesicles with negative surgical margins was not an indication for early adjuvant therapy. A slowly rising PSA (PSA doubling time >12 months) in the absence of positive surgical margins or positive lymph nodes was interpreted as local relapse for which the patient was treated with pelvic irradiation (60 Gy). A PSA persistence in the presence of negative surgical margins and any steep rising PSA (PSA doubling time ≤12 months) after a period of undetectable nadir were both considered a sign of occult metastasis. Therefore, these patients were treated with endocrine treatment.

## 3. Results

Patient characteristics are described in Table 1. Mean age of the patients was 61.8 years (SD 7.0). Mean PSA was 13.7 ng/mL (range <0.02–97.0). Mean follow-up of the study was 98 months (range 7–162). Twenty patients (14.4%) had undergone previous pelvic surgery: inguinal hernia repair in 19 and surgery for pelvic fracture in one. Twelve patients (8.6%) had received neoadjuvant HT prior to surgery. No patient had undergone pelvic radiotherapy. In our population of 139 patients, mean operative time was 105 minutes (range 50–180) with a mean blood loss of 558 mL

(range 100–2100). The urethral catheter was removed at day 12 (range 10–15). Mean admission time was 12 days (range 5–27).

*3.1. Complications and Functional Results.* Preoperatively, no ureteral or vascular injury occurred. Operative complications included one sectioning of the obturator nerve (0.7%) and one rectal laceration (0.7%). Treatment consisted of microsurgical repair of the obturator nerve and primary closure of the rectal laceration in a double layer. Long-term evolution was uneventful in both cases. No peri-operative mortality was noted.

In the peri-operative period no ureteral obstruction or urinary retention occurred. In 10 patients (7.2%) healing of the abdominal wound was delayed: 6 wound infections (4.3%) and 4 partial wound dehiscences (2.9%) occurred. Prolonged drainage in the suction drains was noted in 5 patients. Lymphatic leakage was present in 3 cases (2.2%). Two patients (1.4%) had a urinary leakage for 36 hours which resolved spontaneously with permanent suction. Prolonged drainage did not show to be prognostically relevant since all 5 patients obtained total continence at 12 months. All above mentioned patients were discharged without reintervention.

When lower urinary tract symptoms were present, a uroflowmetry was performed: within 12 months, 4 patients (2.9%) were diagnosed with an anastomotic stricture. One patient complained of a painful orgasm. Urethroscopy visualised a surgical clip at the level of the anastomosis. After removal of the clip, the dysorgasmia disappeared.

At 12 months, 98 patients were completely continent (70.5%) and 24 patients mentioned an occasional loss of a drip (17.3%). Incontinence for which protective pads were needed was only seen in 17 patients (12.2%). Of these 17 patients, one had already been treated for overactive bladder. Only 6 of these 17 patients needed more than one pad per day (4.3%). And only 2 of them complained of continuous and uncontrollable incontinence: an artificial urinary sphincter was therefore implanted (1.4%). Postoperative potency was evaluated at 12 months. 129 patients were treated by a non-nerve-sparing RP. 83.6% mentioned absence of erections; 10.4% experienced some tumescence, but not sufficient for vaginal intercourse, and 6% patients had erections, sufficient for successful vaginal intercourse. Mean age of these last patients was only 54.5 years (range 49.8 to 62.2 years). In the 10 patients who were treated with a unilateral nerve sparing procedure, erections did not recur in 40% and did recur partially though insufficiently for vaginal intercourse in 50%; 10% regained full erectile function.

Table 2 [11–16] compares the operative characteristics, peri-operative complications and mortality, late postoperative complications, and functional results of our present series of RP in locally advanced PCa with major series of RP in clinically localized PCa [11–15] and 1 series of RP in locally advanced PCa (Lerner) [16]. Mean blood loss ranged from 600 to 872 mL in the organ-confined series, which compares favourably with our series (558 mL) and the series by Lerner (945 mL). Rectal, ureteral, and obturator nerve injury occurred in 0.3–4.9%, 0.1–0.8%, and 0.3–1.6%, respectively, in the organ-confined PCa series. These results again compare favourably with the present series (0.7%, 0%, and 0.7%, resp.). In the series by Lerner, only rectal injury was mentioned (1.8%), while ureteral and obturator nerve injuries were not. Wound problems ranged from 0.9 to 13.8%, while reinterventions were rare at 0.5–1.7%. Again, this was not different in our series (7.2% and 0%, resp.) and the series by Lerner (2.7% and NA, resp.). Nonsurgical complications varied, but were infrequent, both in the literature reviewed as in the present analysis. Long-term complications (measured at 12 months) were mainly anastomotic strictures (range 0.7–13.8%) and incontinence, requiring pad use (12–20%). These were comparable to our series (2.9% and 12.2%, resp.) and the Lerner series (9.2% and 22.1%, resp.).

*3.2. Oncologic Outcomes.* At final histopathology, in 19 patients, positive surgical margins were found (13.7%). Of these specimens with positive surgical margins, 2 tumours were organ confined (pT2), 12 showed extraprostatic extension (pT3a), 4 were invading the seminal vesicles (pT3b), and one had invaded the bladder neck (pT4). Table 3 provides an overview on the percentage of positive section margins according to the pathologic stage. In 14 patients, positive lymph nodes were found (10.1%). 13 were staged as clinical N0 by contrast-enhanced CT scan ($n = 12$) or MRI scan ($n = 1$). In one patient, preoperative lymph node staging was not performed because of PSA <10 ng/mL and biopsy Gleason score <7.

Postoperative evaluation included history, physical examination, and serum PSA measurement. PSA persistence (>0.02 ng/mL) at first follow-up was found in 14 patients (10.1%). These cases were considered surgical failures. In 10 of these 14 patients (71.4%), final histopathology revealed positive surgical margins or positive lymph nodes. Within one year, 10 patients (7.2%) underwent RT of the pelvis and 19 patients (13.7%) were started on endocrine treatment because of positive surgical margins, PSA persistence, or rising PSA (Table 1). At a mean follow-up of 98 months (median 98, range 7–162), 35.5% of the patients had received adjuvant or salvage RT and 38.8% of the patients had received adjuvant or salvage HT.

The long-term oncologic outcomes were assessed by Kaplan-Meier survival estimates. The 10-year estimated biochemical progression-free survival, clinical progression-free survival, cancer specific survival, and overall survival rates were 51.8%, 85.6%, 94.6%, and 85.9%, respectively, (Figures 1(a)–1(d)).

## 4. Discussion

Treatment options for locally advanced PCa vary and the jury is still out regarding the optimal treatment [17]. Watchful waiting, RT, HT, surgery, and combinations have been proposed.

In cT3 PCa, Thompson reported a 60 to 70% 5-year overall survival with watchful waiting [18]. Similarly, Johansson et al. mention a 15-year progression-free survival rate of 46.6% and a disease-specific survival rate of 56.5% [19].

Table 2: Complication rates after open radical retropubic prostatectomy.

| | Joniau | Dillioglugil et al. [11] | Hisasue et al. [12] | Gaylis et al. [13] | Maffezzini et al. [14] | Lepor et al. [15] | Lerner et al. [16] |
|---|---|---|---|---|---|---|---|
| Number of patients | 139 | 472 | 123 | 116 | 300 | 1000 | 812 |
| cT1 % (pT1 %) | 0 | 20.3 | 44.7 | 43 | (0) | 78.5 | 0 |
| cT2 % (pT2 %) | 0 | 72.7 | 55.3 | 57 | (66.4) | 21.3 | 0 |
| cT3 % (pT3 %) | 100 | 6.9 | 0 | 0 | (29.9) | 0.2 | 100 |
| Mean age (years) | 62.0 | 63 | 66 | 66.6 | 65.5 | 60.3 | |
| Mean operation time (min) | 105 | | | 155 | | | |
| Mean blood loss (mL) | 558 | | | 872 | 600 | | 945 |
| Mortality % | 0 | | | 0 | 0 | | 0.4 |
| Rectal injury % | 0.7 | 0.6 | 4.9 | 0.9 | 0.3 | 0.5 | 1.8 |
| Ureteral injury % | 0 | 0.2 | 0.8 | | 0.3 | 0.1 | |
| Iliac vessel injury % | 0 | 1.1 | | | | | |
| Obturator nerve injury % | 0.7 | 0.2 | 1.6 | | 0.3 | | |
| Angor/myocardial infarction % | 0.7 | 1.7 | | | | 0.6 | 0.4 |
| Other cardiac complications % | 0 | 10.6 | 0.8 | | | 0.2 | |
| Pulmonary complications % | 0 | 3.8 | | | | 0.1 | |
| Deep venous thrombosis/pulmonary embolism % | 0 | 2.3 | 0.8 | 3.4 | 0.3 | 0.3 | 4 |
| Gastrointestinal complications % | 0 | 5.1 | 0.8 | | | 0.6 | |
| Neurological complications % | 1.4 | 1.5 | | | | 0.2 | |
| Other infectious complications % | 0 | 4.7 | 0.8 | | | | 0 |
| Prolonged drainage (urine, lymph, blood) % | 3.6 | 2.8 | 8.9 | | 2 | 0.7 | 0.8 |
| Acute retention % | 0 | 0.6 | | | 2 | | |
| Reintervention % | 0 | | | | 1.7 | 0.5 | |
| Woundproblem % | 7.2 | 3.0 | 13.8 | 0.9 | 1 | 0.8 | 2.7 |
| Anastomotic stricture at 12 months % | 2.9 | | 13.8 | | 0.7 | 1 | 9.2 |
| Not dry (in need of pads) at 12 months % | 12.2 | | 12.7 | 20 | 12 | | 22.1 |

Table 3: Comparison between positive surgical margins and pathologic staging after radical retropubic prostatectomy.

| | Positive surgical margins |
|---|---|
| All patients | 13.7% |
| pT2 | 4.8% |
| pT3a | 17.4% |
| pT3b | 18.2% |
| pT4 | 50% |

cT3 PCa is therefore regarded as a significant tumour with a considerable associated mortality, especially in patients with a long life expectancy. Thus, watchful waiting is only allowed in a strict minority of selected patients with a poor general health status [18, 19].

Until the early eighties, radiotherapy was the treatment of choice for localized and locally advanced PCa. With radiotherapy as monotherapy, 10-year disease-free survival rates of 19–44% and overall survival rates of 21–54% have been reported [20–23]. At 25-year follow-up, radiotherapy as monotherapy only added a neglectable gain in survival. When patients did not die of intercurrent disease, they were highly likely to develop recurrence and to die of PCa [20].

In an attempt to improve disease-free survival and overall survival, the combination of RT and HT was evaluated. Laverdiere et al. had indeed shown a significant improvement in oncological outcome with adjuvant HT [24]. These findings were corroborated in randomised trials of the European Organisation for Research on Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG) [25, 26]. The EORTC trial 22863 turned out to be a milestone study. Disease-specific survival and overall survival rates at 5 years improved from 79% to 94% and from 62% to 78%, respectively, in favour of combined RT and HT. Neoadjuvant HT was evaluated in the RTOG 86-10 trial. A significant decrease in local and distant progression and a significant increase in disease-free survival and disease-specific survival were noted at a mean follow-up of 8 years. However, overall survival did not increase significantly [27].

By many, the combination of external-beam RT and adjuvant HT is since considered a standard therapeutic option in patients with cT3 PCa.

Literature on the value of RP as an option for cure in cT3 PCa is limited. However, clinical evidence showing 5-year disease-specific survival rates ranging between 85% and 100% is available [28–31]. Additionally, RP can prevent local tumour-associated complications and provide a clear

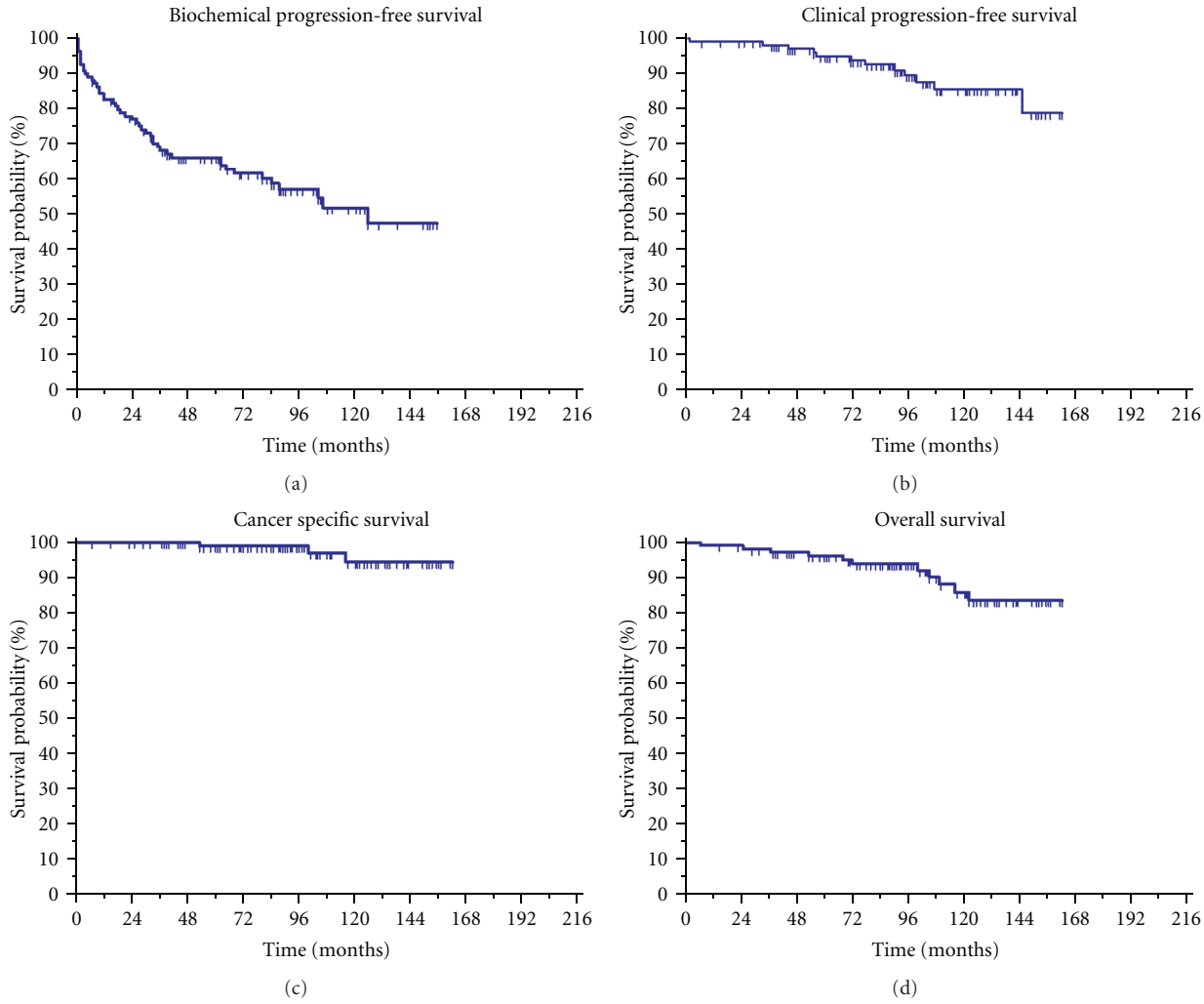


Figure 1: Kaplan-Meier plots for the oncologic outcomes of surgery for cT3a-b PCa. (a) Biochemical progression-free survival. (b) Clinical progression-free survival. (c) Cancer-specific survival. (d) Overall survival.

Table 4: The percentage of overstaging and understaging in clinical locally advanced T3 prostate cancer.

| Authors | pT2 | pT4/N+ |
|---|---|---|
| Van Poppel et al. [28] | 13% | 8%/11% |
| Van den Ouden et al. [29] | 15% | 3.4%/15.6% |
| Lerner et al. [16] | 17% | —/33% |
| Morgan et al. [32] | 22% | 42% (stage D1) |
| Ward et al. [33] | 27% | —/27% |

definition of failure after therapy compared to the more vaguely defined failure parameters after RT. Furthermore, overstaging of cT3 PCa ranges from 13 to 27% (pT2) (Table 4) [16, 28, 29, 32–34]. In pT2, RP has a very high chance of cure and long-term outcome after RP is very good [34].

Some locally advanced PCa will not be cured by surgery alone, and therefore, combinations with hormone therapy or radiotherapy have been investigated. Neoadjuvant HT did not improve biochemical or clinical progression, nor survival rates in RP [35–37]. Adjuvant HT after RP has shown to be beneficial, especially in poor prognosis disease [16]. Early adjuvant RT has also shown a lower risk of local recurrence, a longer time to progression, and an improved cancer-specific and overall survival [10, 38]. This effect was also more pronounced in high-risk patients: EORTC trial 22911 showed a clear improvement of progression-free survival and local control in patients with positive surgical margins or pT3 prostate cancer when RP was combined with RT [10]. Recently, long-term follow-up of cT3 PCa treated primarily with a prostatectomy has been published. Majority of patients underwent adjuvant RT and/or HT. 5-, 10-, and 15-year disease-free survival and disease-specific survival rates were 85%, 73%, and 67% and 95%, 90%, and 79%, respectively [33].

The general impression is that complications such as rectal injury, haemorrhage, deep venous thrombosis, pulmonary embolism, urinary fistula, ureteral obstruction, stress incontinence, impotence, anastomotic stricture, and perioperative death are more common in the cT3 patient group. Our review of literature shows that the mortality risk associated with RP is merely a theoretical risk. Other

surgery-related complications such as rectal injury, ureteral obstruction, and injury to the iliac vessels or obturator nerves are encountered rarely and do not account for a significant amount of morbidity. At an incidence between 0.6% and 7.3%, all of these per-operative complications could be resolved during the same operation. Long-term consequences such as anastomotic strictures occur in 0.7% to 13.8% of patients. One single dilatation has a success rate of up to 75% [12, 14]. Another late problem is incontinence. In 12% to 22.1% of patients, at least one protective pad is still needed at 12 months [11–16, 33].

In Table 2, we compare the complication rates and functional results of our series of 139 cT3 PCa patients with some major contemporary RP series in organ-confined and 1 series of RP in locally advanced PCa. Postoperative complications are grouped according to organ system. With absent mortality, a peri-operative complication rate of 1.4%, and postoperative complication rate of 12.9%, our cT3 population is exposed to an equal risk of complications compared to patients who undergo an RP for cT1 or cT2 tumours. At the same time, our results compare favourably with those mentioned by Lerner in RP for locally advanced PCa. The only paper which has so far directly compared surgical complications in locally advanced PCa versus localized disease in a single institution is from Gontero et al. The two groups did not differ significantly in surgical morbidity except for blood transfusion, operative time, and lymphoceles, which showed a higher rate in patients with advanced disease [39]. We corroborate these results in our present analysis.

Furthermore, in our series, functional results at 12 months show total continence (no pad necessary) in 87.8% and socially acceptable continence (max. 1 precautionary pad) in 94.2%, which is well within acceptable ranges. Finally, anastomotic stricture was encountered at a rather low rate of 2.9%. Expectedly, potency rates were poor in non-nerve-sparing RP (6% full recovery at 1 year and 10% partial recovery), while those rates were better in unilateral nerve-sparing RP (10% full recovery and 50% partial recovery). As complete recovery of erectile function can take up to 36 months, further improvement of these results may be expected [40]. Furthermore, modern imaging (Magnetic Resonance Imaging (MRI), diffusion-weighted MRI) allows more accurate preoperative assessment of tumour invasion in the neurovascular bundle, further increasing the indications for a nerve-sparing approach [41].

Surgical margins after RP are of great importance in progression and oncological outcome [42–46]. Margin positive status varies between 29% and 60.5% in the corresponding articles. The lowest incidence of positive margins was 29% and was found in a population of predominantly organ-confined PCa (73.7% pT2) [42]. In our series of cT3 PCa, 31.1% were pT2. Positive surgical margins were found in only 13.7%, which is the lowest rate in literature to our knowledge. It is clear, though, that surgery for locally advanced PCa had a considerable learning curve. At our institution, the learning curve translated into a dramatic decrease in positive margin rates from 66.7% in the period 1987–1994 to 43.3% in the period 1995–1999 to 10.0% in the period 2000–2004 [7].

Our present analysis is not devoid of limitations. First, this is a retrospective analysis of complications and functional results, using data extracted from patient files. Inherent biases are to be expected, as sometimes more discrete complications can be missed. Second, preoperative data on the functional status of the patient were not collected, limiting the interpretation of the results. Third, the complications and functional results were compared to data extracted from the literature. Indeed, a more solid approach would be to prospectively compare data on RP in cT3a-b PCa with data on RP in localized disease from the same institution. Nevertheless, we believe that our analysis has its value in outlining the incidence of complications and the functional results that can be expected after RP for locally advanced PCa. It has to be stressed that data on this subject are extremely scarce. Finally, a significant number of patients received adjuvant or salvage RT and/or HT treatment following surgery, limiting the interpretation of the results regarding the value of surgery in locally advanced PCa. Accepting this limitation, oncologic control with RP as a first step in the treatment of locally advanced PCa is excellent.

## 5. Conclusion

Our experience with 139 patients confirms the surgical feasibility of RP for cT3 PCa, showing complication rates comparable with RP in organ-confined PCa and showing a very low incidence of positive surgical margins and associated failure of surgery. Improvement can be expected by further defining the patient population most suitable for surgery and by further optimising adjuvant treatments such as RT and HT. Continence rates were also comparable with those achieved after RP for localized PCa. A nerve-sparing approach was only considered possible in a limited number of patients. It has to be expected, though, that modern imaging will further increase the indications for nerve-sparing surgery in locally advanced PCa.

Prospective randomized clinical trials are needed to compare oncological outcome, treatment-related complications, and quality of life in the different treatment options for cT3 PCa.

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*Clinical Study*

# Oncologic Outcomes of Surgery in T3 Prostate Cancer: Experience of a Single Tertiary Center

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*Aim*. The aim of this study is to present the oncologic outcomes and to determine the prognostic factors of overall survival (OS), cancer-specific survival (CSS), disease-progression-free survival (DPFS), and biochemical-progression-free survival (BPFS) after surgery for pT3 prostate cancer (PCa). *Methods*. Between 2002 and 2007, a pT3 stage after radical prostatectomy was detected in 182 patients at our institution. The Kaplan-Meier analysis was used to calculate OS, CSS, DPFS, and BPFS. Cox regression was used to identify predictive factors of survival. *Results*. pT3a was detected in 126 (69%) and pT3b in 56 (31%) of cases. Five-year OS, CSS, DPFS, and BPFS rates were 90.7%, 94%, 91.8%, and 48.4%, respectively. Survival was significantly different when comparing pT3a to pT3b groups. The 5-year OS, CSS, DPFS, and BPFS were 96% versus 72%, 98% versus 77%, 97.3% versus 79.3%, and 60% versus 24.2%, respectively. Specimen Gleason score was the most significant predictor of OS, CSS, DPFS, and BPFS. The risk of death increased up to 3-fold when a Gleason score 8–10 was present at the final pathology. *Conclusions*. Radical prostatectomy may offer very good CSS, OS, DPFS, and BPFS rates in pT3a PCa. However, outcomes in patients with pT3b or specimen Gleason $\geq 8$ were significantly worse, suggesting the need for multimodality treatment in those cases.

## 1. Introduction

During the last decade, the definition of the optimal treatment in high-risk prostate cancer (PCa) has been among the topics that are of most interest to the urological community, but consensus in this field is still not reached. Up until a decade ago, most T3 PCa patients underwent radiotherapy (RT) or androgen deprivation therapy (ADT) or a combination of both, while only about 36% were initially treated by surgery [1]. Recent publications have revealed that in selected cases of locally advanced and high-grade tumours, surgery as monotherapy or as part of a multimodality treatment may be used instead of RT [2]. The high-risk PCa population, usually described as having prostate specific antigen (PSA) >20 ng/mL, biopsy Gleason score ≥8, or an advanced clinical stage (T3a-b) [3], is however not homogeneous. Recent studies have shown that treatment outcomes can vary widely, depending on whether patients present with only one or rather a combination of those high-risk factors, with the latter patients having the worst outcomes [4–7]. It is still unclear which patients, according to the accepted predictors of aggressive disease behaviour, are the best candidates for surgery, mostly due to the lack of data on long-term oncologic outcomes and randomized clinical trials. According to the European Association of Urology guidelines, surgery is optional in patients presenting with cT3a, Gleason score 8–10, or PSA >20 ng/mL and life expectancy of more than 10 years [8]. Even in highly selected patients with cT3b or cN1 PCa, surgery may be offered as part of a multimodality approach [8]. We believe that radical prostatectomy is indeed an appropriate treatment for more aggressive PCa, but data for confirming that are still insufficient.

The purpose of this study is to present the oncologic outcomes of patients having pT3a and pT3b PCa after surgery, including overall survival (OS), cancer-specific survival (CSS), disease-progression-free survival (DPFS), and biochemical-progression-free survival (BPFS). Furthermore, we aimed to analyze predictive parameters in survival.

## 2. Material and Methods

During the period 2002–2007, 840 radical retropubic prostatectomies (RRP) were performed in our tertiary referral institution. 192 of them had pathological stage T3 (22.9%). Ten patients were lost for additional followup. Final analysis was carried out using the data of 182 patients with complete followup. No patients received neoadjuvant treatment. The last PSA before biopsy was used for analysis.

Biopsy Gleason score ≥7, PSA >10 ng/mL, or clinical stage T3 was indication for lymph node removal. 113 of 182 (62.1%) patients of our study population had such criteria. For the other 69 (37.9%) patients, a lymphadenectomy was not performed.

The pathological examination of radical prostatectomy specimens and bilateral pelvic lymph nodes was performed by one dedicated uropathologist.

Serum PSA and physical examination were performed every 3 months in the first year after surgery, every 6 months in the second and third years, and annually thereafter. The PSA data were taken from outpatient clinic files. Data about patients' death and cause of death were received from the National Cancer Registry.

OS was defined as the time from surgery to death from any cause. CSS was defined as the time from surgery to death caused by PCa or complications of this disease. Biochemical progression was defined as the time from surgery to PSA level ≥0.2 ng/mL confirmed by repeated test. Disease progression was defined as the development of either local disease recurrence or distant metastasis. Adjuvant treatment was defined as either ADT or RT given within 3 months after surgery. Salvage treatment was defined as any kind of therapy (RT or ADT) given later than 3 months after surgery. The main indication for adjuvant treatment was positive lymph nodes. Combination of Gleason score ≥8, preoperative PSA >20 ng/mL, pT3b, and positive surgical margins were other indicators for adjuvant treatment.

The Kaplan-Meier survival analysis was used to calculate the OS, CSS, DPFS, and BPFS. The differences were tested by log-rank test. The Cox regression analysis was used to determine the prognostic factors for survival.

## 3. Results

An overview of the patients' preoperative and postoperative parameters is shown in Table 1. The median followup was 54 months (range 6–96). 5-year rates for OS, CSS, DPFS, and BPFS in our study cohort were 90.7%, 94%, 91.8%, and, 48.4%, respectively. Cox regression analysis revealed that from all parameters (age, biopsy and surgery Gleason score, surgical margin and lymph node status, pathological stage, and preoperative PSA level) only pathological stage and postoperative Gleason score had an impact on overall mortality and disease progression (Table 2). The Gleason score also has the strongest impact on CSS. According to Cox regression analysis, there were no other parameters influencing cancer specific mortality (Table 2). Pathological stage, lymph node status and postoperative Gleason score were the strongest prognostic factors for biochemical disease progression (Table 2).

*3.1. Lymph Node Status.* A mean of 6.4 (range 1–15) lymph nodes were removed, and the overall positive node detection rate was 10.6%. During the study period, the overall mortality rate in pN1 patients was 50% and cancer-specific mortality rate was 33.3%. Patients with pN0 or pNx had significantly lower overall (6.9% and 5.8%, resp.) and cancer-specific mortality rate (5.0% and 2.9%, resp.). The Kaplan-Meier analysis showed that 5-year OS (93% versus 40%, Figure 1(a)), CSS (95% versus 50%, Figure 1(b)), and DPFS (96.5% versus 92.6% versus 40.7%) rates were significantly different when comparing pNx, pN0, and pN1, respectively. There was no difference between pNx and pN0 in survival analysis. PSA relapse rate was different comparing patients with pN1, pN0, and pNx. 5-year BPFS was 0% in pN1 group, 43.4% in pN0, and 65.3% in pNx groups (Figure 1(c)).

*3.2. Pathological Stage.* The Kaplan-Meier analysis showed that pT3a and pT3b stages provide significantly different 5-year OS (96% versus 72%, resp.; Figure 2(a)), CSS (98% versus 77%, resp.; Figure 2(b)), DPFS (97.3% versus 79.3%, resp.) and BPFS (60% versus 24.2%, resp.; Figure 2(c)). Positive lymph nodes were found significantly less frequently in pT3a (2 of 71, 2.8%) than pT3b PCa (10 of 42, 23.8%) ($P = 0.0001$). Lymph node positivity did not impact survival in the stage pT3a PCa, but had a significant role in the stage pT3b PCa. Estimated 5-year OS, CSS, and DPFS rates in pT3bN1 (38%, 50%, and 38.6%, resp.) were significantly worse ($P = 0.0001$) compared with pT3bN0-Nx (84%, 88%, and 86.2%, resp.). 5-year BPFS rate was 31% in patients with pT3bN0-Nx while all patients with pT3bN1 had biochemical relapse during the study period.

*3.3. Gleason Score.* During the study, close correlation between pathological stage and cancer differentiation was established. The mean biopsy Gleason score was significantly worse in pT3b compared to pT3a PCa (6.8 versus 6.4, $P = 0.001$) and after surgery (7.5 versus 6.9, $P = 0.001$). Gleason score upgrading was detected in 52.5% of cases and downgrading in 5.6% of cases. Increased Gleason score was correlated with an increased positive lymph node rate: 29.2% at Gleason ≥8 versus 5.7% at Gleason ≤7 ($P = 0.003$). The Kaplan-Meier analysis demonstrates significant differences between Gleason ≤7 and ≥8 for OS (Figure 3(a)), CSS (Figure 3(b)), DPFS, and BPFS (Figure 3(c)) in the total study population. The estimated 5-year OS, CSS, DPFS, and BPFS rates in patients with Gleason score ≥8 were 61%, 64%, 62.4%, and 13.5%, respectively, while in Gleason score ≤7, 5-year OS, CSS, DPFS, and BPFS were 96%, 99%, 97.8%, and 56.3%, respectively.

*3.4. Surgical Margin Status.* Positive surgical margin (R1) rate was significantly different ($P = 0.03$) comparing pT3a to pT3b cases (Table 1). Although in Cox regression this parameter was not determined as prognostic factor for survival the Kaplan-Meier analysis demonstrated different 5-year CSS (98.6% versus 90%, log-rank $P = 0.047$) and BPFS (55.9% versus 44.2%, log-rank $P = 0.08$) rates comparing R0 to R1 in all study population. Impact of surgical margin status on outcome was analyzed separately in patients who

Table 1: Patient characteristics.

| Parameter | pT3a ($N = 126$, 69.2%) | pT3b ($N = 56$, 30.8%) | All ($N = 182$, 100%) |
|---|---|---|---|
| Median age (yr) (range) | 66.5 (49–78) | 65 (48–76) | 66 (48–78) |
| Median PSA (ng/mL) (range) | 7.63 (0.68–39.89) | 11.6 (3.1–98.4) | 8.67 (0.68–98.4) |
| Mean biopsy Gleason (range) | 6.4 (6–9) | 6.8 (5–10) | 6.5 (5–10) |
| Gleason ≤6 | 68.3% | 41.1% | 59.8% |
| Gleason 7 | 26.0% | 41.1% | 30.7% |
| Gleason ≥8 | 5.7% | 17.9% | 9.5% |
| Mean surgery Gleason (range) | 6.9 (6–9) | 7.5 (6–9) | 7.1 (6–9) |
| Gleason ≤6 | 19.8% | 3.6% | 14.9% |
| Gleason 7 | 71.4% | 58.2% | 67.4% |
| Gleason ≥8 | 8.8% | 38.2% | 17.7% |
| *R* (%) | 54.2% | 71.7% | 59.5% |
| *N*+ (rate) | 2.8% (2/71) | 23.8% (10/42) | 10.6% (12/113) |
| PSA relapse | 29.6% | 75.0% | 43.6% |
| Deaths (rate) | 3.2% (4/126) | 23.2% (13/56) | 9.3% (17/182) |
| Deaths from cancer (rate) | 0.8% (1/126) | 17.9% (10/56) | 6% (11/182) |
| mts | 2.4% | 17.9% | 7.1% |
| Median followup (mo) (range) | 56 (7–96) | 50.5 (6–94) | 54 (6–96) |

Table 2: Cox multivariate regression analysis of preoperative and histopathologic parameters.

| Parameter | Overall survival | | | Cancer-specific survival | | | Biochemical progression free survival | | |
|---|---|---|---|---|---|---|---|---|---|
| | HR | 95% CI | *P* value | HR | 95% CI | *P* value | HR | 95% CI | *P* value |
| Pathological stage | 0.195 | 0.052–0.735 | 0.016 | 0.00 | 0.00–9.80 | 0.923 | 0.475 | 0.291–0.775 | 0.003 |
| Age | 1.06 | 0.977–1.152 | 0.162 | 1.068 | 0.943–1.208 | 0.29 | 1.005 | 0.969–1.043 | 0.779 |
| Lymph node | 0.546 | 0.158–1.88 | 0.337 | 0.832 | 0.166–4.276 | 0.823 | 0.715 | 0.542–0.943 | 0.018 |
| Pre operative PSA | 1.013 | 0.982–1.046 | 0.406 | 1.007 | 0.964–1.051 | 0.766 | 1.005 | 0.991–1.019 | 0.490 |
| Surgical margins | 0.878 | 0.220–3.514 | 0.855 | 0.522 | 0.058–4.686 | 0.562 | 0.756 | 0.440–1.30 | 0.312 |
| Biopsy Gl. score | 1.072 | 0.600–1.915 | 0.814 | 1.093 | 0.530–2.251 | 0.81 | 1.077 | 0.792–1.466 | 0.636 |
| Surgery Gl. score | 2.82 | 1.492–5.337 | 0.001 | 3.24 | 1.018–10.311 | 0.04 | 2.029 | 1.461–2.818 | 0.0001 |

did not receive adjuvant treatment. Only 5-year BPFS rate was different comparing patients with R0 to those with R1: 62.3% versus 52.5% (log-rank $P = 0.023$), respectively.

*3.5. Postoperative Treatment.* Patients with pT3 PCa are generally considered at risk for disease progression. Therefore, adjuvant or salvage treatment (RT or ADT) is often applied. In our study population, additional treatment was given to 32.4% (adjuvant to 15.9% and salvage to 16.5%) of cases: 21.4% in the pT3a and 57.1% in the pT3b subgroups. 20.3% of patients received ADT, 7.1% RT, and 5% RT with ADT. All twelve patients with N1 received adjuvant treatment: two of them received RT with ADT and the other ten ADT alone.

## 4. Discussion

During the last decade, the discussion about the role of surgery in locally advanced PCa became increasingly active. Before that time, treatment of locally advanced PCa was mostly in hands of radiation oncologists [1]. Such discussion became possible for several reasons: successful treatment of high-risk PCa with RT monotherapy requires high radiation doses (74–80 Gy), leading to higher rates of adverse events. On the other hand, recent studies [2, 9–12] demonstrate outcomes after surgery which can be compared with radiation therapy +/− ADT. Our single center study shows that surgical treatment may indeed be a reasonable treatment option in locally advanced PCa with 90.7% OS and 94% CSS at the 5-year follow-up mark. Surgery in pT3a PCa, independently of cancer differentiation and PSA level demonstrated significantly higher 5-year OS, CSS, DPFS, and BPFS rates when compared to pT3b disease (96% versus 72%, 98% versus 77%, 97.3% versus 79.3%, and 60% versus 24.2%, resp.). The survival rates of the pT3a patients in our study are similar to those reported by Hsu et al. in a study of 200 patients with unilateral cT3a treated by surgery. They also showed that progression-free survival rates of patients with pT3a PCa did not differ significantly from those with pT2 disease [7]. Some other authors have also reported their outcomes of surgical treatment for T3 PCa. Summarizing those results, 5-year CSS and OS rates varied from 85 to 100% and from 75 to 98%, respectively [9–12]. Direct comparison between the outcomes of surgery and radiation is inadequate because of inherent selection biases, Gleason score upgrading, or stage migration after surgery. Nevertheless, this issue could be partially solved using data

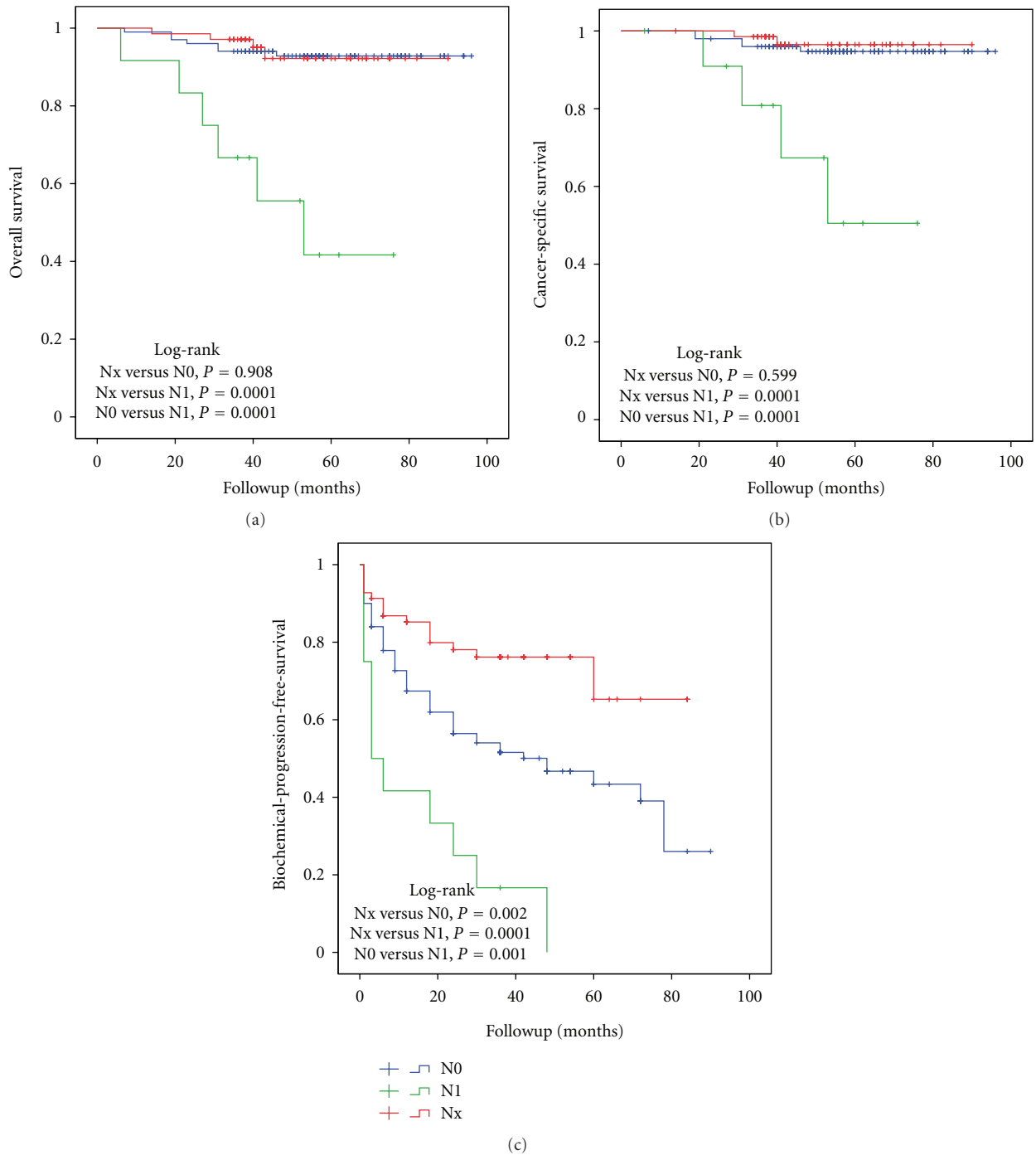


Figure 1: The Kaplan-Meier analysis with log-rank test for overall (a), cancer-specific survival (b), and biochemical-progression-free survival (c) stratified for lymph node status.

from the RTOG trials which compared RT to a combined approach using RT and ADT [13]. In a review of those RTOG trials, different PCa risk groups were identified with group 2 (Gleason ≤6, T3Nx-N1 or Gleason 7, T1-2Nx) and group 3 (Gleason 7, T3Nx-N1 or Gleason ≥8, T1-2Nx) most closely corresponding with our study population. After radiation, the 5-year OS and CSS rates were 82% and 94% for group 2 and 68% and 83% for group 3, respectively [13]. Outcomes from another long-term study comparing RT to RT with concomitant ADT were reported by Bolla et al. [14]. In the EORTC trial, 412 patients with locally advanced PCa were treated with RT alone or in combination with ADT. Five-year OS and CSS rates were, respectively, 62 and 79% in the radiation-alone group. Better survival was reported in

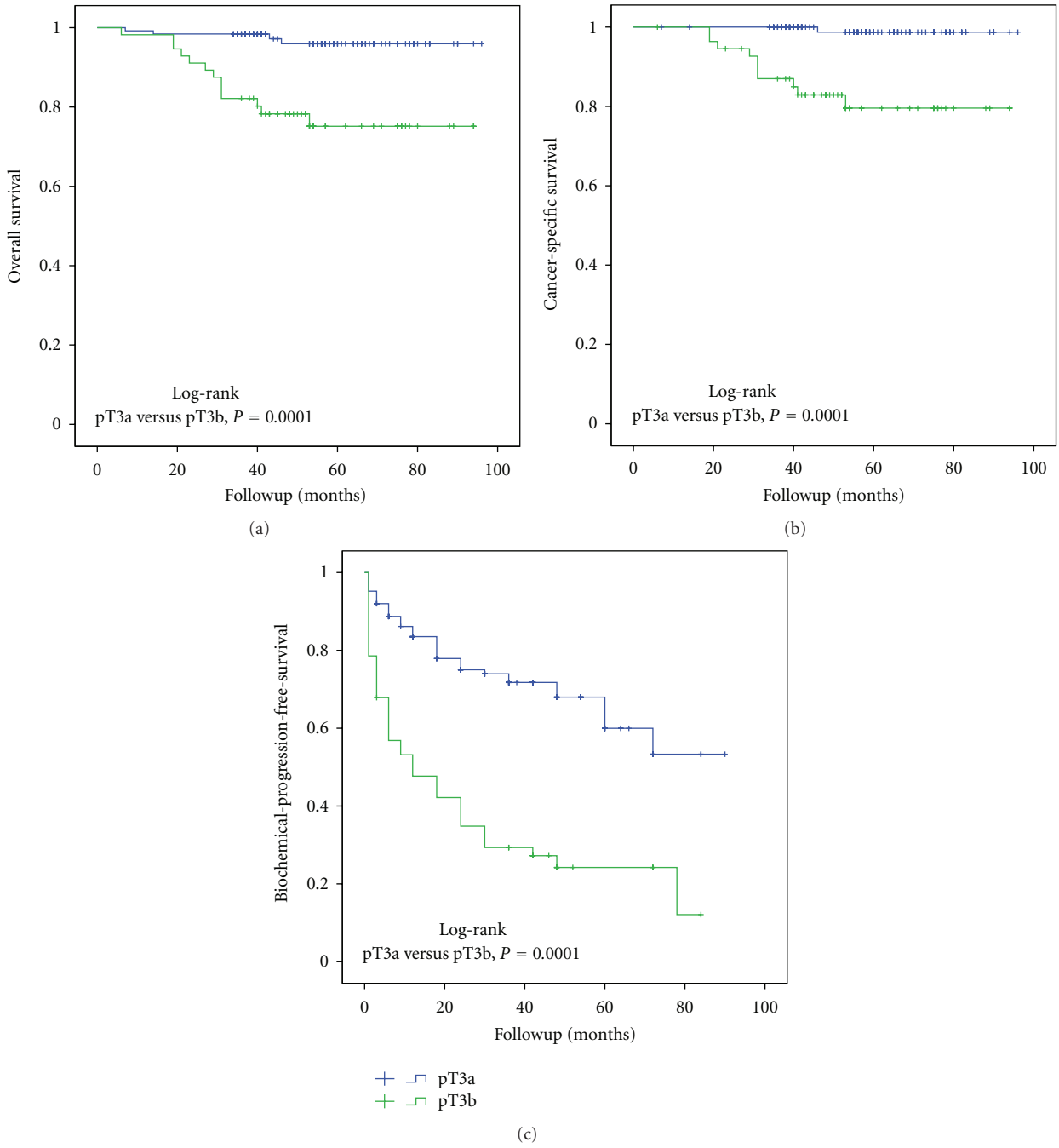


Figure 2: The Kaplan-Meier analysis with log-rank test for overall (a), cancer-specific survival (b), and biochemical-progression-free survival (c) stratified for pathological stage.

combination group: 78% and 94%, respectively. Our study data showed a comparable 94% 5-year CSS, similar to RT and ADT combination therapy.

The group of locally advanced PCa is heterogeneous. PSA and specimen Gleason score have a significant impact on the survival analysis. According to our study, pT3a patients with a PSA <10 ng/mL had significantly better OS and BPFS when compared to those with a PSA level >20 ng/mL (log rank $P = 0.048$ and $P = 0.0001$, resp.). Patients with a PSA level of 10 to 20 ng/mL did not have significantly different OS when compared to PSA <10 or PSA >20 ng/mL (log rank $P = 0.552$) but had different BPFS compared to PSA >20 ng/mL (log rank $P = 0.008$). In the pT3a group, PSA had no impact on CSS and DPFS. In the pT3b group, we found no significant impact of PSA level on the 5-year OS, CSS, or DPFS. A possible explanation for this observation could be the variable application of adjuvant therapies. 5-year BPFS rate in the pT3b group was different comparing

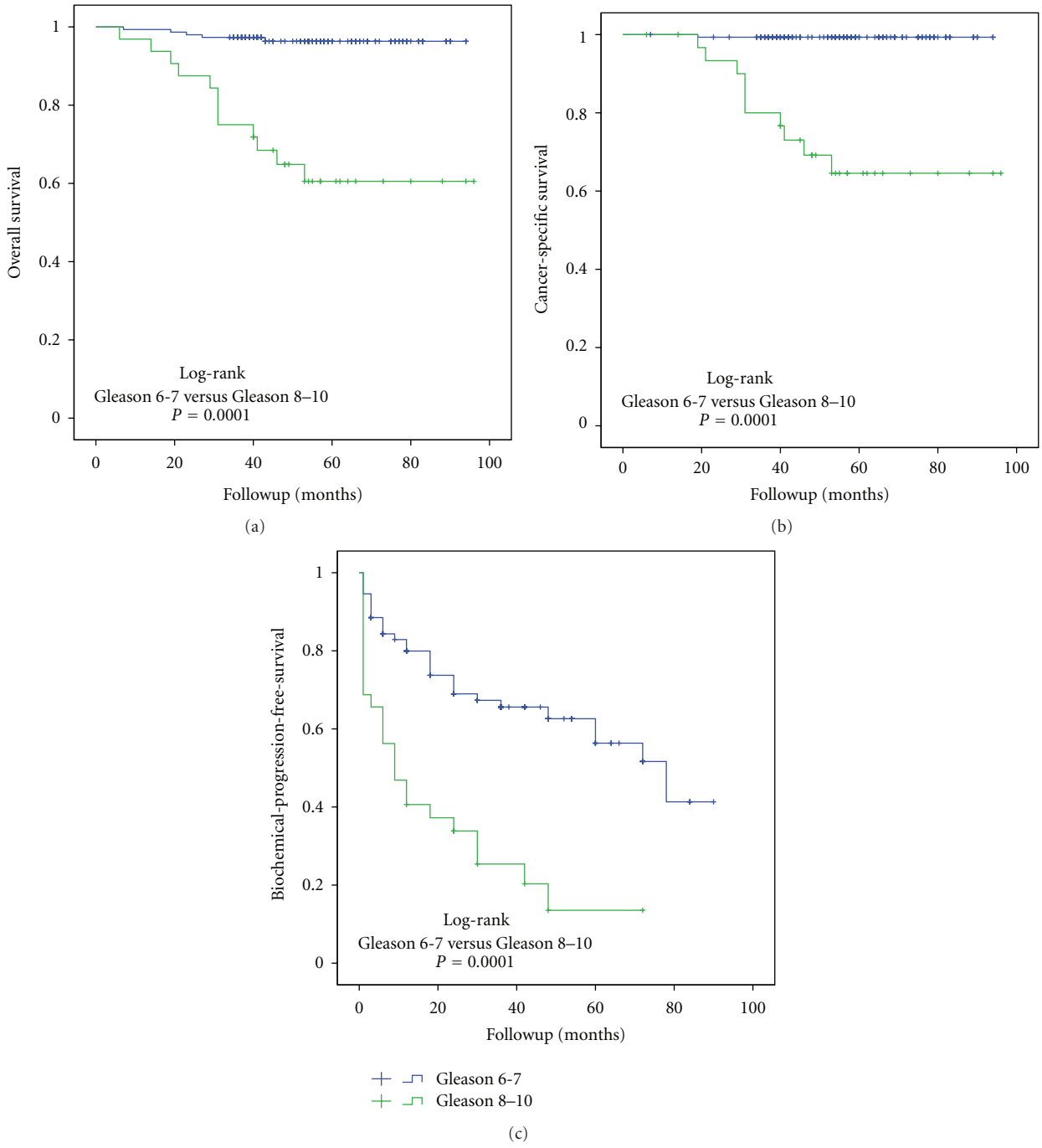


Figure 3: The Kaplan-Meier analysis with log-rank test for overall (a), cancer-specific survival (b), and biochemical-progression-free survival (c) stratified for Gleason score sum.

patients with PSA >20 to <10 ng/mL (log rank $P = 0.019$). Some recent studies also studied the role of PSA in survival and biochemical or disease progression [4, 5, 15]. All authors agreed that PSA >20 ng/mL indeed could be considered as a high-risk factor. Our findings support that patients with PSA >20 ng/mL had significantly worse BPFS and OS but not CSS or DPFS rates in pT3 PCa population.

Gleason score has long been recognized as an important risk indicator for worse outcome. In locally advanced PCa, biopsy Gleason sum has a tendency to be upgraded, and in our series upgrading was indeed frequent (up to 50%). In fact, in our study, specimen Gleason score was identified as the most important outcome predictor. Our data showed a significant difference between survival curves comparing Gleason score 5–7 to 8–10. More importantly, patients with postoperative Gleason ≥8 are associated with a 2.8-fold increased risk of death and 2.4-fold increased risk of disease progression. If cancer differentiation after surgery is ≥8, the

risk of death from cancer increases more than 3-fold. Gleason score 8–10 is also associated with a higher node-positive rate when compared with Gleason score 7 (6.3% versus 4.5%, chi-square test $P = 0.03$). Most of the published studies confirm that Gleason score 8–10 indeed determines worse biochemical or disease-free survival [6, 16, 17] both in locally advanced and organ-confined disease [18]. Our study shows that 5-year OS, CSS, DPFS, and BPFS rates in Gleason score 8–10 PCa were 61%, 64%, 62.4%, and 13.5% compared to 96%, 99%, 97.8%, and 56.3% if Gleason score was 5–7. However, significant survival differences between high- and moderate-grade PCa do not mean that a more advanced tumor grade is a contraindication for surgery. Tewari et al. pointed out that long-term results in high-grade PCa after surgery are better when comparing surgically treated patients with those who underwent RT or conservative treatment [19]. In 453 patients with biopsy Gleason 8–10, median OS after surgery was 9.7 years, while for radiation this was 6.7 years and for conservative treatment 5.2 years. The risk of cancer-related death after surgery was 68% lower than after conservative treatment and 48% lower than after RT.

The pT3b stage is associated with the poorest oncological outcomes after surgery. In our study, the rate of positive margins was 71.7%, while 23.8% and 38.2% had pN1 disease and specimen Gleason score 8–10, respectively. These adverse pathological outcomes are directly related to the oncological outcomes: 5-year CSS was 77%, OS was 72%, DPFS was 79.3%, and BPFS was 24.2%. A subanalysis of T3b patients without positive lymph nodes (pT3bN0-Nx) showed 5-year OS, CSS, DPFS, and BPFS rates of 84%, 88%, 94%, and 52.1%, respectively. There are no possibilities to compare the results of surgery and RT in such small cohort of patients. If we look to the outcomes (5-year OS rates >75% and CSS >85%) of radical prostatectomy at advanced stage and high-grade PCa in large review presented by Van Poppel and Joniau [2], our pT3b survival data are similar. This suggests that not all patients with cancer extending into the seminal vesicles are destined to have poor outcomes. Lymph node status and Gleason score seem to play the most important role in pT3b PCa outcomes.

From our analysis the presence of positive surgical margins was not significant predictor for survival in Cox regression. The Kaplan-Meier analysis showed that only 5-year BPFS was different comparing R0 to R1 in all study cohort (55.9% versus 44.2%, log rank $P = 0.08$). We found similar data excluding patients who received adjuvant treatment. Only BPFS was different comparing surgical margin status. The similar findings were reported by Hsu et al. [7]. Authors concluded that margin status was a significant independent predictor in BPFS but did not influence OS, CSS, and DPFS. The question remains if patients with positive margins should receive adjuvant treatment in pT3 cases. Our study data confirms that R1 with Gleason $\geq 8$ is proper candidate for adjuvant treatment, but more randomized studies are needed to cover this topic.

Generally, it is accepted that patients with locally advanced PCa at final histology are ideal candidates for additional treatment after surgery. Up until now, there is still no consensus on which treatment modality—RT, ADT, or a combination—is the best choice to decrease the risk of disease progression following surgery. In the present study, only 32.4% of cases (21.4% in pT3a and 57.1% in pT3b) received additional treatment: 15.9 received adjuvant and 16.5% salvage treatment. Cox regression analysis did not show impact of adjuvant therapy on survival, but we were unable to investigate real influence of adjuvant treatment on outcomes because of small number of cases and not randomized study design. According to our data, 42.9% of patients in pT3b and 78.6% in pT3a did not receive any additional treatment during median 4.5-year followup. It shows that surgery as monotherapy could be discussed with patient even in suspected T3 PCa.

With 5-year OS, CSS, DPFS, and BPFS of 91%, 94%, 91.8%, and 48.4%, our study supports the notion that radical prostatectomy with adjuvant or salvage therapy as RT plus ADT when needed may provide comparable outcomes in locally advanced PCa, especially in pT3a. However, this finding should be confirmed in prospective, randomized studies.

## 5. Conclusions

Radical prostatectomy may offer very good CSS, OS, DPFS, and BPFS rates in pT3a PCa. However, outcomes in patients with pT3b or specimen Gleason $\geq 8$ were significantly worse, suggesting the need for multimodality treatment in those cases.

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*Clinical Study*

# Clinical Results after High-Dose Intensity-Modulated Radiotherapy for High-Risk Prostate Cancer

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*Purpose*. Patients with high-risk prostate cancer (PC) can be treated with high-dose intensity-modulated radiotherapy (IMRT) and long-term androgen deprivation (AD). In this paper we report on (i) late toxicity and (ii) biochemical (bRFS) and clinical relapse-free survival (cRFS) of this combined treatment. *Methods*. 126 patients with high-risk PC (T3-4 or PSA > 20 ng/mL or Gleason 8–10) and ≥24 months of followup were treated with high-dose IMRT and AD. Late toxicity was recorded. Biochemical relapse was defined as PSA nadir +2 ng/mL. Clinical relapse was defined as local failure or metastases. *Results*. The incidence of late grade 3 gastrointestinal and genitourinary toxicity was 2 and 6%, respectively. Five-year bRFS and cRFS were 73% and 86% respectively. AD was a significant predictor of bRFS ($P = 0.001$) and cRFS ($P = 0.01$). *Conclusion*. High-dose IMRT and AD for high-risk PC offers excellent biochemical and clinical control with low toxicity.

## 1. Introduction

The of PSA screening has resulted in an increased detection rate of prostate cancer (PC) with stage migration towards lower-stage prostate cancer (PC). Nevertheless, still 12% of the patients with PC will have locally advanced (T3-4 N0 M0 or Tx N1 M0) or metastatic disease at diagnosis [1]. More aggressive therapies are indicated for these patients as they are at increased risk of PC death [2]. External beam radiotherapy (EBRT) is one of the standard treatment options of choice for those patients. However, when conventional low-dose (<72 Gy) EBRT is applied in patients with clinical stage T3-T4 PC, local recurrence rates mount to 30% at 10 years [3]. Improvement of local control is important as local failure is directly correlated with distant metastasis [3, 4] and survival [5]. Extensive evidence exists that high-dose radiotherapy (dose ≥ 74 Gy) is superior to conventional dose radiotherapy (dose 64–70 Gy) [6–8]. For high-risk patients, an increase in 5-year biochemical relapse-free survival (bRFS) of 19% has been reported when increasing the dose from 70 Gy to 80 Gy [9]. Zelefsky et al. demonstrated that the rate of positive biopsies after EBRT dropped with 30% when the dose was increased from <70.2 Gy to >81 Gy [10]. With modern radiotherapy techniques, such as intensity-modulated radiotherapy (IMRT), dose escalation can safely be performed [11]. Randomized trials support the combined use of EBRT and androgen deprivation (AD) with superior disease-specific and overall survival outcomes in patients with locally advanced-stage or high-risk disease [12, 13].

Based on the above-mentioned data, patients with high-risk PC are treated at our institute with high-dose IMRT and 24–36 months of AD. In this paper, we report on

(i) late gastrointestinal (GI) and genitourinary (GU) toxicity,
(ii) biochemical control,
(iii) clinical control

of this combined treatment modality.

## 2. Material and Methods

*2.1. Patients.* Between December 1998 and March 2011, 604 patients were treated with IMRT as primary therapy

for prostate cancer at Ghent University Hospital (GUH). Over time 3 different dose levels were initiated as has been previously reported [14, 15]. Between 1996 and 2001, 2 prescriptions were launched: 74 Gy (74R72) and 76 Gy (76R74) as median dose to the planning target volume (PTV) of the prostate + seminal vesicles with a hard constraint on maximal rectal dose of 72 and 74 Gy, respectively. In 2002, a third dose escalation level was initiated, in which we treated the PTV to 78 Gy while keeping the maximal rectal dose at 76 Gy (78R76).

High-risk PC was defined as PC with one of the following characteristics: clinical T3-4 or PSA >20 ng/mL or Gleason 8–10. Patients with pN1 or cN1 disease were treated within another study protocol [16] and consequently not included in this study. In total 43% of the patients fulfilled these criteria. Only patients with high-risk PC and a minimal followup of 24 months were considered for this report resulting in a study population of 126 patients: 21 patients in the 74R72 group, 19 patients in the 76R74 group, and 86 patients in the 78R76 group.

T stage was determined by digital rectal examination supplemented with magnetic resonance (MR) imaging data. The 2002 American Joint Commission on Cancer staging was used [17]. Lymph node staging was done by CT scan in all cases and in 54 cases by pelvic lymphadenectomy. All patients underwent bone scintigraphy. Except for 10 patients, who refused AD, a luteinizing-hormone releasing hormone (LHRH) analogue was initiated for a period of 24–36 months.

A fixed questionnaire was used to register the medical history and pretreatment GU and GI symptoms of each patient.

*2.2. Treatment Planning.* Details on pretreatment imaging, delineation of clinical target volume (CTV) and organs at risk, expansion of CTV to PTV, treatment planning, criteria for plan acceptance, leaf position optimization, patient preparation, and treatment delivery can be found in our previous work [14]. In brief, the CTV consisted of the prostate and seminal vesicles. None of the patients received elective lymph node irradiation. The PTV was created using a 3-dimensional, isotropic expansion of the CTV of 7 mm. The rectal wall (excluding air and faeces), sigmoid colon, bladder, small bowel, and femoral heads were delineated as organs at risk. Patients were treated with empty rectum and comfortably filled bladder.

The dose was prescribed as the median dose to the PTV. Treatment was delivered using 18 MV photons of an Elekta linear accelerator (Crawley, UK) equipped with a multileaf collimator (MLC) and able to deliver IMRT in a step-and-shoot mode. Since 2009, patients were also treated on a Clinac ix (Varian Medical Systems, Palo Alto, Calif, USA). Until 2009, 3 beams with gantry angles 0°, 116°, and 244° were used [8]. Thereafter, planning was performed with 7 beams (gantry angles: 0°, 52°, 103°, 154°, 206°, 257°, and 308°) or with single arc therapy (1 full arc counter clockwise) [18]. First, a fixed couch height and portal imaging procedure (Elekta electronic portal imaging device) was used to correct patient positioning. Thereafter, an ultrasound-based (SonArray, Zmed, Ashland, USA), prostate positioning was added to correct for prostate positioning. Since 2009, positioning is performed by daily kilovoltage cone beam CT.

*2.3. Followup.* Patients were seen every 3 months for the first year, biannually until 5 years, and yearly thereafter. A fixed toxicity questionnaire was fulfilled at each visit.

*2.4. End Points. Late toxicity* was defined as any increase of any GI or GU toxicity lasting more than 3 months after cessation of IMRT or occurring for the first time later than 3 months after the end of IMRT. The grade of late GI (Table 1(a)) and GU toxicity (Table 1(b)) was scored according to an in-house developed scoring system based on the RTOG, SOMA/LENT, and CTC toxicity scorings system [19, 20]. For each symptom, the maximal toxicity score was registered.

*Biochemical relapse* was defined according to the Phoenix consensus definition, that is, PSA nadir +2 ng/mL [21].

*Clinical relapse* was defined as local failure (determined on prostate biopsies) or metastases (both lymph node and haematogenous metastasis) detected on imaging (18F-fluorodeoxyglucose positron-emitting tomography/computed tomography and bone scan) performed at the time of biochemical relapse.

Kaplan-Meier statistics were used to report on 5-year bRFS and clinical relapse-free survival (cRFS). Univariate analysis (log-rank test) was used to examine the predictive value of the dose prescription group, Gleason score group (Gleason 6 versus 7 versus 8–10), cT (T1-T2-T3-T4), PSA (PSA $<$ 10 ng/mL versus PSA: 10–20 ng/mL versus PSA $\geq$ 20), staging by lymphadenectomy (pN0 versus pNx), and use of AD. Multivariate analysis was performed using Cox regression analysis.

Using *Chi-square statistics*, the baseline patient-related risk factors were compared for the different prescription groups. A $P$ value of $< 0.05$ was considered statistically significant.

Statistical analysis was performed with SPSS version 15.0 software (Chicago, ILL, USA).

## 3. Results

Patient characteristics and planning parameters are shown in Tables 2 and 3, respectively. Significantly fewer patients received AD in prescription group 74R72 ($P = 0.002$). Except for follow-up time, all other parameters were equally balanced between the different prescription groups. Median followup was 48 months.

*3.1. Late Toxicity.* Late toxicity was mild. No patient developed grade 4 GI or GU toxicity. The incidence of grade 1–3 late GI and GU toxicity is presented in Table 4. The crude incidence of late grade 3 GI and GU toxicity was 2 and 6%, respectively. Dose escalation did not result in increased GI or GU toxicity.

Table 1: (a) The in-house developed Gastrointestinal toxicity scale, (b) The in-house developed Genitourinary toxicity scale.

(a)

| GI | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Abdominal cramps | Present, no therapy | Peroral therapy, for example, Spasmolytic | IV therapy | Surgery |
| Diarrhea | Present, no therapy | Peroral therapy, for example, loperamide | IV therapy | Surgery |
| Frequency | Present, no therapy | Peroral therapy, for example, loperamide | IV therapy | — |
| Mucus loss | Present, no therapy | Need hygienic pads | Continuous, invasive therapy | Surgery |
| Red blood loss | No therapy, frequency < 3x/week | Frequency ≥ 3x/week | Invasive therapy needed, for example, laser coagulation | Transfusion need, surgery |
| Urgency | Present, no therapy | Peroral therapy | IV therapy | — |
| Incontinence | Present, no therapy | Need hygienic pads (≤2/day) | Need hygienic pads (>2/day) | Surgery |
| Anal pain | Present, no therapy | Local anesthetic for example, Xylogel | Narcotic analgetica | Surgery |

(b)

| GU | Grade 1 | Grade 2 | Grade 3 | Grade 4 |
|---|---|---|---|---|
| Nocturia | Twice pretherapy, 2-3 times | 4–6 times (<1x hour) | >6 times (more frequently than hourly) | — |
| Frequency | Once/2 h, twice pretherapy | Once/1 h | Once/0.5 h (more frequent than hourly) | — |
| Hematuria | Microscopic | Intermittent/moderate | Frequent, gross hematuria/minor surgery needed (coagulation) | Hemorrhagic cystitis requiring transfusion/ ulceration/ necrosis |
| Dysuria | Slight, no medication | Moderate, requiring local anesthetic (including bladder spasm) | Dysuria, regular and frequent narcotics needed (including bladder spasm and pelvis pain)/severe/ stenosis/TUR or dilatation | Bladder obstruction not secondary to clot passage |
| Urgency | Slight, no medication | Moderate, requiring local anesthetic (including bladder spasm) | Severe requiring local anesthetic | — |
| Incontinence | <weekly episodes | <daily episodes | Pads/undergarments/ day | Refractory |

*3.2. Biochemical Relapse.* Twenty-eight patients experienced biochemical relapse resulting in a 5-year bRFS of 73% for the whole group. T stage, addition of lymphadenectomy, pretreatment PSA, and Gleason score were not significantly correlated with bRFS. Although not significant, there was a strong trend towards better 5-year bRFS rates with higher radiotherapy doses (52%, 83%, and 76% for 74R72, 76R74, and 78R76, resp., $P = 0.051$) (Figure 1).

The association of AD was significantly correlated with 5-year bRFS (77% versus 30%; $P < 0.001$) (Figure 2).

In multivariate analysis AD remained a significant predictor of bRFS ($P = 0.001$).

*3.3. Clinical Relapse.* Fourteen patients had a clinical relapse. Clinical relapses occurred in the lymph nodes ($N = 4$), bone ($n = 9$), or prostate ($n = 2$). One patient had both lymph node and bone metastases at time of clinical relapse. The 5-year cRFS was 86%. T stage, addition of lymphadenectomy, pretreatment PSA, and Gleason did not significantly influence cRFS. There was a significant correlation between 5-year

Table 2: Patient's characteristics for all patients and according to prescription group.

| Characteristic | Prescription group | | | |
|---|---|---|---|---|
| | All ($n$ = 126) | 74R72 ($n$ = 21) | 76R74 ($n$ = 19) | 78R76 ($n$ = 86) |
| Age (years) | 66 (41–79) | 62 (51–76) | 65 (53–75) | 66 (41–79) |
| Followup (months) | 48 (24–132) | 60 (24–132) | 84 (24–108) | 45 (24–96) |
| PSA level (ng/mL) | 19 (4–302) | 26 (8–150) | 20 (4–90) | 14 (4–302) |
| Gleason score | | | | |
| 2–6 | 49 (39) | 9 (43) | 11 (58) | 29 (34) |
| 7 (3 + 4)/(4 + 3) | 37 (29) | 7 (33) | 5 (26) | 25 (29) |
| 8–10 | 39 (31) | 5 (24) | 3 (16) | 31 (36) |
| Unknown | 1 (1) | — | — | 1 (1) |
| Tumor stage | | | | |
| T1 | 17 (13) | 2 (10) | 4 (20) | 11 (12) |
| T2 | 40 (32) | 9 (43) | 2 (11) | 29 (34) |
| T3 | 60 (48) | 7 (33) | 12 (64) | 40 (48) |
| T4 | 9 (7) | 3 (14) | 1 (5) | 6 (6) |
| Node stage | | | | |
| pN0 | 54 (43) | 9 (43) | 3 (16) | 42 (49) |
| Androgen deprivation | | | | |
| Yes | 116 (92) | 14 (67) | 17 (89) | 85 (99) |
| No | 10 (8) | 7 (33) | 2 (11) | 1 (1) |

Table 3: Planning parameters for all patients and according to prescription. CTV: clinical target volume; Gy: Gray; PTV: planning target volume; R40 and R60: percentage of the rectal volume receiving a dose of 40 and 60 Gy, respectively; $R_{mean}$: mean dose to the rectum, $B_{max}$ and $B_{mean}$: maximal and mean dose to the bladder.

| | All ($n$ = 126) | 74R72 ($n$ = 21) | 76R74 ($n$ = 19) | 78R76 ($n$ = 86) |
|---|---|---|---|---|
| CTV volume (cc) | 61 (22–180) | 86 (26–146) | 68 (28–112) | 53 (22–180) |
| Minimum CTV dose (Gy) | 73 (55–77) | 68 (55–70) | 72 (67–74) | 73 (68–77) |
| Median CTV dose (Gy) | 78 (72–83) | 76 (72–78) | 77 (72–82) | 79 (74–83) |
| PTV volume (cc) | 155 (48–347) | 250 (121–347) | 226 (100–289) | 123 (48–296) |
| Minimum PTV dose (Gy) | 69 (52–73) | 65 (52–68) | 67 (65–70) | 69 (64–73) |
| Median PTV dose (Gy) | 77 (70–82) | 74 (70–76) | 75 (72–80) | 78 (75–82) |
| R40 | 71 (30–97) | 90 (88–90) | 87 (57–97) | 68 (30–94) |
| R60 | 43 (22–90) | 64 (29–90) | 54 (26–69) | 40 (22–63) |
| $R_{mean}$ | 51 (33–71) | 57 (39–65) | 54 (37–62) | 49 (33–71) |
| $B_{max}$ | 79 (72–82) | 78 (72–79) | 79 (76–82) | 79 (76–82) |
| $B_{mean}$ | 43 (13–72) | 49 (19–68) | 58 (16–65) | 40 (13–72) |

Table 4: Late gastrointestinal and genitourinary toxicity for all patients and according to prescription group.

| | Late GI toxicity | | | |
|---|---|---|---|---|
| | All ($n$ = 126) | 74R72 ($n$ = 21) | 76R74 ($n$ = 19) | 78R76 ($n$ = 86) |
| Grade 1 | 52 (41) | 9 (43) | 8 (42) | 35 (41) |
| Grade 2 | 20 (16) | 6 (29) | 2 (11) | 12 (14) |
| Grade 3 | 2 (2) | 0 | 1 (5) | 1 (1) |
| | Late GU toxicity | | | |
| | All ($n$ = 126) | 74R72 ($n$ = 21) | 76R74 ($n$ = 19) | 78R76 ($n$ = 86) |
| Grade 1 | 55 (44) | 11 (52) | 7 (37) | 37 (43) |
| Grade 2 | 26 (21) | 1 (5) | 4 (21) | 21 (24) |
| Grade 3 | 7 (6) | 3 (14) | 1 (5) | 3 (4) |

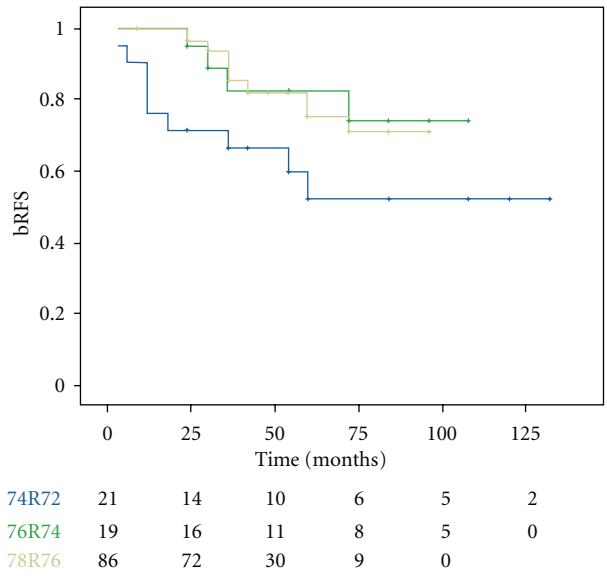


Figure 1: Biochemical relapse-free survival according to prescription group.

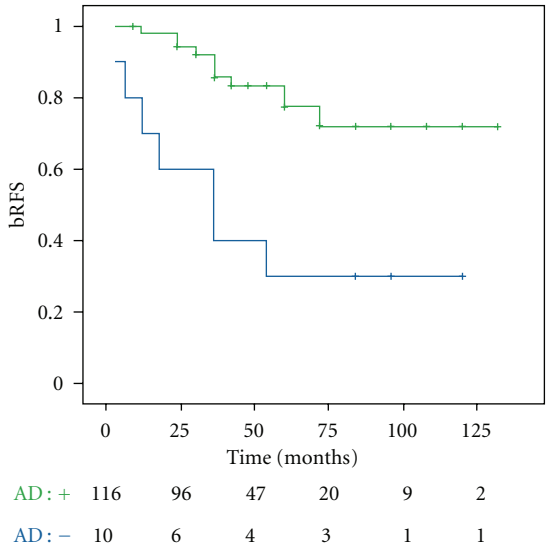


Figure 2: Biochemical relapse-free survival for patients treated with high-dose IMRT with or without androgen deprivation.

cRFS and dose (67%, 83%, and 90% for 74R72, 76R74, and 78R76, resp.; $P = 0.04$) as well as between 5-year cRFS and AD (91% versus 30%; $P < 0.001$).

The only significant predictor of cRFS in multivariate analysis was AD ($P = 0.01$).

## 4. Discussion

Multiple treatment options are available for patients with high-risk PC such as surgery, high-dose EBRT, and AD.

AD has been the primary treatment for patients with high-risk PC for many years. Although the response rate is high, AD alone is not a curative therapy and has important side effects. A recently published randomized trial confirmed that the addition of EBRT to AD resulted in a significant improvement in overall survival when compared to AD [22].

Merglen et al. claimed that surgery, as a single treatment, offers the best 10-year survival rates for T1–T3 PC patients when compared to EBRT without AD, particularly for younger patients and patients with poorly differentiated tumours [23]. However this study has major shortcomings such as the lack of information on radiation dose and an imbalance between the surgery and radiotherapy group concerning Gleason score and PSA [23]. Moreover, 10-year overall survival and PC-specific survival was better for patients treated with EBRT and AD versus prostatectomy alone (80% versus 69% and 87% versus 83% for overall survival and PC-specific survival, resp.).

Akakura et al. randomized patients between radical prostatectomy and low-dose EBRT (60–70 Gy) both combined with AD. The 10-year overall survival rates were better for the surgery group, although not statistically significant [24]. Recently the long-term outcome of patients with high-risk PC was reported comparing survival after RP and EBRT ± AD. The authors concluded that RP and EBRT + AD provided similar long-term cancer control for patients with high-risk PC [25]. In a retrospective matched case analysis, RP, brachytherapy, and multimodality radiotherapy (i.e., EBRT with brachytherapy boost and AD) were compared. Significantly improved bRFS at 4 years was reported with multimodality radiotherapy (multimodality radiotherapy: 72%, brachytherapy: 25%, and RP: 53%, $P < 0.001$) [26]. In the absence of randomized trials and based on published data surgery, whether or not combined with adjuvant radiotherapy and high-dose radiotherapy combined with AD should be considered as equally effective in this patient group.

In the published series, clinical or biochemical relapse is still observed in more than a quarter of the patients 5 years after treatment. Extensive evidence exists that high-dose radiotherapy (dose ≥ 74 Gy) is superior to conventional dose radiotherapy (dose 64–70 Gy). Zelefsky et al. reported long-term results after high-dose radiotherapy for T3 PC. For patients treated with high doses (81 Gy) combined with AD, 5- and 10-year PSA relapse-free survival was 77% and 52% for T3a stage and 53% and 49% for T3b stage PC. Dose was an important predictor of improved biochemical control. With higher doses (≥ 81 Gy), 5- and 10-year local progression-free survival of 96% and 88% is reported [27].

Our data confirm these encouraging figures with 5-year bRFS and cRFS rates of 73% and 86%, respectively. In contrast with the study of Zelefsky et al., we were not able to detect a significant dose-response relationship. Although there was a significant relation between prescription dose and cRFS and a strong trend towards better bRFS with higher doses, this was no longer present in multivariate analysis. These data must be interpreted with caution due to the small number of patients in the lowest prescription group as well as the imbalance between the patients receiving AD in the different prescription groups. Significantly fewer patients in prescription group 74R72 received AD. The role of concomitant AD was unequivocally confirmed in our

study with a significant impact on bRFS and cRFS in uni- and multivariate analysis.

Dose escalation to the prostate is only defendable if both radiotherapy-induced GI and GU toxicities remain acceptable. There is level 1 evidence that toxicity increases with dose when conventional or conformal radiation technologies are used [11]. The implementation of new radiotherapy technologies has resulted in low GI toxicity rates. Even with dose escalation to the prostate late grade ≥3 GI toxicity is rare with modern radiotherapy techniques with incidence rates of <1% [28] to 2% [29] and 5% [30]. On the contrary, GU toxicity is more frequent with incidence rates of late grade ≥ 3 GU toxicity of 13% [30]. The reported toxicity rates in our study (grade 3 GI: 2% and grade 3 GU: 6%) are comparable with published data and confirm that high-dose IMRT combined with AD can safely be delivered. Dose escalation did not result in higher toxicity rates in our study probably as a result of the implementation of a direct aperture and weight optimization (SOWAT) in the higher prescription groups. In a planning study, the use of SOWAT resulted in a reduction of the rectal complication probability by lowering the physical dose to rectal volumes without compromising the dose to the prostate. The present paper confirms that SOWAT is clinically relevant and makes further dose escalation possible without increasing rectal or urinary toxicity.

The role of prophylactic pelvic irradiation for patients with high-risk PC is still under debate. Two large randomised trials were published with opposite results. The Radiation Therapy Oncology Group (RTOG) 9413 trial favours pelvic radiotherapy [31]. A significant 7% improvement in the 4-year progression-free survival (PFS) rate was reported when patients were treated with a combination of neoadjuvant + concurrent AD and pelvic EBRT compared with prostate-alone EBRT for patients with intermediate and high-risk PC. However, there was no significant benefit in overall or distant metastases-free survival. Importantly, an increase in late grade 2 and 3 toxicities was noted [31].

The GETUG randomised trial on the contrary failed to show differences in PFS [32].

There are 2 important shortcomings of these "older" trials that might have influenced the results: at first, the radiotherapy dose to the prostate was low (70 Gy). Secondly there might have been an insufficient coverage of the pelvic lymph nodes regions at risk. The role of dose was evaluated in the GETUG trial in which they failed to show a significant difference in the groups receiving < or ≥ 70 Gy at the level of the prostate, which is, after all, still a low dose [32].

A large retrospective study with high-dose brachytherapy also failed to demonstrate a benefit for pelvic irradiation, suggesting that dose escalation to the prostate rather than pelvic radiotherapy is beneficial [33].

A new phase III trial (RTOG 0924) will soon be opened for enrolment further addressing the issue on prophylactic pelvic irradiation. The RTOG 0924 is a phase III trial for intermediate and favourable high-risk PC patients randomizing between androgen deprivation and high-dose radiotherapy with or without whole pelvic radiotherapy. PIVOTAL is another multicentre study for patients with locally advanced PC randomising between high-dose IMRT to the prostate ± pelvic lymph nodes. The endpoints of the study are toxicity, quality of life, and disease outcome. Patient recruitment is now ongoing.

In the absence of the results of these "modern" phase III trials, the implementation of pelvic irradiation is not current standard and left at the discretion of the radiotherapists. In our study only 4 patients had a clinical relapse in the lymph nodes making the omission of prophylactic pelvic radiotherapy defendable certainly when taking into account the increased risk of GI toxicity as a result of irradiation of larger volumes of small bowel, even with modern radiotherapy techniques.

Some recent data suggest that the patient's outcome is positively influenced by staging lymphadenectomy. However, the exact impact of an extended lymphadenectomy on patient outcomes has not yet been clearly determined. Recently, Masterson et al. reported that a higher number of nodes removed correlated significantly with bRFS in men without nodal involvement [34] probably as a result of elimination of micrometastases that are not detected by routine histological examination. Joslyn and Konety [35] published similar results. Patients included in this study were treated since 1996. At that time staging lymphadenectomies were not routinely performed. Consequently only few patients in our study received a staging pelvic lymphadenectomy. Moreover, there is an important lack of information on extent of lymphadenectomy and number of lymph nodes removed. In our study 3 of the 4 patients presenting with lymph node relapse did not have previous lymphadenectomy.

## 5. Conclusion

High-dose IMRT and AD for high-risk PC offers excellent biochemical and clinical control with low toxicity.

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*Review Article*

# Management of High-Risk Localized Prostate Cancer

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Traditionally, patients with high-risk localized prostate cancer have been an extremely challenging group to manage due to a significant likelihood of treatment failure and prostate cancer-specific mortality (PCSM). The results of multiple large, prospective, randomized trials have demonstrated that men with high-risk features who are treated in a multimodal fashion at the time of initial diagnosis have improved overall survival. Advances in local treatments such as dose-escalated radiotherapy in conjunction with androgen suppression and postprostatectomy adjuvant radiotherapy have also demonstrated benefits to this subset of patients. However, therapeutic enhancement with the addition of chemotherapy to the primary treatment regimen may help achieve optimal disease control.

## 1. Introduction

Prostate cancer is the most common noncutaneous malignancy and is the second leading cause of cancer-related mortality among men in the USA [1]. In 2010, it is estimated that 217,730 men were newly diagnosed and 32,050 men died of prostate cancer [2]. Simply stated, roughly 1 in 6 American men will be confronted with a diagnosis of prostate cancer during their lifetime. Prostate cancer exhibits a broad spectrum of clinical behaviors, ranging from microscopic, well-differentiated indolent tumors to aggressive malignancies with significant potential for recurrence and metastasis. Most prostate cancers are localized at the time of diagnosis which is likely to continue with increasing emphasis on screening and improving technology for early detection.

Historically, patients with localized prostate cancer were categorized primarily based on clinical staging and whether or not they were considered surgical candidates. Thus, the term "localized" generally referred to stage T1-T2 disease which was managed with local therapy (surgery, radiotherapy) or active surveillance. "Locally advanced" disease referred to stage T3-T4 disease which was considered inoperable. However, a better understanding of the natural history of prostate cancer and advances in both the quality and quantity of available treatment options have allowed clinicians to develop more sophisticated risk stratification systems (Table 1).

Current risk stratification of prostate cancer patients is based upon the likelihood of recurrence after locoregional treatment (Table 2). Various pretreatment parameters have been studied as potential prognostic factors to help identify subsets of patients, specifically, among high-risk patients in whom treatment failure is more likely. Prostate-specific antigen (PSA) has been one of the most extensively studied parameters (PSA velocity, PSA doubling time) but remains a source of controversy, particularly with regards to its utility in screening at-risk patients. While PSA can provide general information about the aggressiveness of the tumor or treatment response of a patient's disease, its predictive value alone remains relatively low. The incorporation of pretreatment PSA and the Gleason score in combination with clinical staging has served to better prognosticate patient outcomes. In a multi-institutional study of 4133 prostate cancer patients, combining preoperative serum PSA levels with the Gleason score and clinical stage was able to more accurately predict capsular penetration, involvement of seminal vesicles and pelvic lymph nodes [3]. Several prior studies have confirmed that PSA $> 10$ ng/mL and/or Gleason scores $> 7$ result in a 5-year recurrence risk of approximately 70%. Furthermore, men with high-risk features at presentation

Table 1: Anatomic stage/prognostic groups, high-risk localized prostate cancer.

| Group | T | N | M | PSA | Gleason |
|---|---|---|---|---|---|
| I | T1a–c | N0 | M0 | PSA < 10 | Gleason ≤ 6 |
| | T2a | N0 | M0 | PSA < 10 | Gleason ≤ 6 |
| | T1-2a | N0 | M0 | PSA X | Gleason X |
| IIA | T1a–c | N0 | M0 | PSA < 20 | Gleason 7 |
| | T1a–c | N0 | M0 | 10 ≤ PSA < 20 | Gleason ≤ 6 |
| | T2a | N0 | M0 | 10 ≤ PSA < 20 | Gleason ≤ 6 |
| | T2a | N0 | M0 | PSA < 20 | Gleason 7 |
| | T2b | N0 | M0 | PSA < 20 | Gleason ≤ 7 |
| | T2b | N0 | M0 | PSA X | Gleason X |
| **IIB** | **T2c** | **N0** | **M0** | **Any PSA** | **Any Gleason** |
| | **T1-2** | **N0** | **M0** | **PSA ≥ 20** | **Any Gleason** |
| | **T1-2** | **N0** | **M0** | **Any PSA** | **Gleason ≥ 8** |
| **III** | **T3a-b** | **N0** | **M0** | **Any PSA** | **Any Gleason** |
| **IV** | **T4** | **N0** | **M0** | **Any PSA** | **Any Gleason** |
| | Any T | N1 | M0 | Any PSA | Any Gleason |
| | Any T | Any N | M1 | Any PSA | Any Gleason |

Adapted from American Joint Committee on Cancer (AJCC Cancer Staging Manual, Seventh Edition, 2010).

Table 2: Prognostic factors for recurrence risk in localized prostate cancer.

| Very low | Low | Intermediate | High | Very high (locally advanced) |
|---|---|---|---|---|
| T1c | T1-T2a | T2b-T2c | T3a | T3b-T4 |
| Gleason ≤ 6 | Gleason 2–6 | Gleason = 7 | Gleason 8–10 | |
| PSA < 10 | PSA < 10 | PSA 10–20 | PSA > 20 | |
| <3 (+) biopsy cores w/ ≤ 50% cancer per core | | | | |
| PSA density < 0.15 ng/mL/g | | | | |

Adapted from NCCN Clincal Practice Guidelines in Oncology Prostate Cancer V.1.2011© 2011 National Comprehensive Cancer Network, Inc.

have a significantly higher risk of recurrence, metastatic disease and prostate-cancer-related mortality [4–10].

A recent European multi-institutional study by Spahn et al. highlighted the need to further define the high-risk population in order to deliver the most appropriate therapy to each patient. In this study, 712 high-risk patients with PSA > 20 ng/mL underwent radical prostatectomy with bilateral pelvic lymph node dissection between 1987 and 2005. Patients were stratified into four subgroups based on the number of additional risk factors present (none, biopsy Gleason score ≥ 8, clinical stage 3-4, or both) to assess which risk factors improved prediction of treatment failure and PCSM. The biopsy Gleason score was the strongest predictor of progression and mortality. Among high-risk patients with PSA > 20 ng/mL, those with Gleason scores < 8 had a 10-year PCSM of 5%, while those with Gleason scores ≥ 8 had a PCSM of 35%. Importantly, this study reports that men with PSA > 20 ng/mL and a Gleason score < 8 are at minimal risk for PCSM and may represent a specific subgroup of high-risk patients that should be considered for surgery [11].

Similarly, a retrospective study by Walz et al. reported that the number of risk factors (T3 disease, Gleason ≥ 8, D'Amico high-risk group, PSA ≥ 20 ng/mL) present influences the 5-year biochemical recurrence risk in the postradical prostatectomy setting. The rate of favorable pathology and recurrence after surgical intervention is dependent upon the criteria used to define high-risk disease as well as the conglomeration of risk factors present in each patient [12]. Taken altogether, this suggests that there is still much to learn about high-risk disease and that further characterization of this risk group is necessary in order to optimize treatment.

The most current guidelines define high-risk localized prostate cancer as patients with clinical stage T3 disease, a Gleason score of 8–10 or a PSA level > 20 ng/mL (Table 3). Additionally, the National Comprehensive Cancer Network (NCCN) has defined very high-risk (locally advanced) patients as those with clinical stage T3b and T4 disease without evidence of nodal or metastatic involvement [13–17]. For the purposes of this paper and the discussion of therapeutic management, both high-risk and very high-risk subgroups will be considered together. While no consensus exists with regards to optimal treatment for this subset of patients, it is clear that a multidisciplinary and multimodal therapeutic approach is crucial for proper management of high-risk localized prostate cancer. This paper will focus upon current treatment modalities as well as therapeutic options on the horizon for high-risk patients.

Table 3: Risk stratification for high-risk prostate cancer.

| Source | High-risk definition |
|---|---|
| D'Amico et al. [13] | Stage T2c or PSA > 20 ng/mL or Gleason ≥ 8 |
| RTOG 9902, 0521 [14, 15] | Any T stage, PSA 20–100 ng/mL, Gleason ≥ 7 or stage ≥ T2, PSA < 100 ng/mL, Gleason 8–10 |
| NCCN (v1.2011) [16] | Stage ≥ T3 and/or PSA > 20 ng/mL and/or Gleason 8–10* |

Adapted from Nat Rev Urol 2010 Nature Publishing Group [17]. *Combines high-risk and very high risk (locally advanced) groups.

## 2. Rationale for a Multimodal Approach for the Treatment of High-Risk Prostate Cancer

Traditionally, single modality regimens for treating high-risk patients have resulted in poor treatment responses and high failure rates [18]. These poor clinical outcomes are observed irrespective of the primary treatment type, either a surgical approach with radical prostatectomy (RP) or radiotherapy with external-beam radiation therapy (EBRT) or brachytherapy. A study by Pisansky et al., assessed disease relapse in 500 patients with clinically localized prostate cancer treated solely with radiotherapy. The total RT dose administered was dependent on tumor stage: T1 received a median dose of 64 Gy (range 60–70.7 Gy); T2 64.8 Gy (range, 50–70.2 Gy); T3-4, 66.3 Gy (range, 55.8–70.4 Gy). Amongst high-risk patients, a 24% relapse-free probability at 5 years as well as a much higher incidence of clinical and biochemical relapse was reported when compared to their low and intermediate risk counterparts [19]. Furthermore, a 2005 multi-institutional review by Soloway and Roach further delineated the need to improve existing therapeutic interventions. High-risk patients undergoing monotherapy with curative intent with RP, EBRT, or brachytherapy had high rates of both clinical and biochemical progressions (>50% at 5 years). Importantly, this paper also alluded to the increasing importance of adjuvant therapy and multimodal approaches in order to improve control of high-risk localized disease [20].

## 3. Current Recommendations for Management of High-Risk Prostate Cancer

*3.1. Radiotherapy as a Treatment Option in High-Risk Prostate Cancer.* Technological advances in existing treatment modalities and the combination of local and hormonal therapies have led to considerable progress in disease control and survival outcomes. Radiotherapy has been and will continue to be a key component in the treatment of prostate cancer and much effort has been dedicated to increasing its therapeutic efficacy with new techniques to deliver radiation. The advent of three-dimensional conformal radiation therapy (3D-CRT) and intensity-modulated radiation therapy (IMRT) have allowed radiation oncologists to achieve safe dose escalation while limiting local tissue toxicities classically associated with EBRT, such as genitourinary and bowel complications. Several independent studies have confirmed that dose escalation is associated with improved biochemical outcomes in addition to a lower risk of radiation-associated late side effects [21–25]. A pivotal randomized control trial by Kuban et al. at M.D. Anderson Cancer Center served to validate doses as high as 75–80 Gy as a permissible dose escalation for the high-risk cohort. Among the 301 patients enrolled in this long-term study, the subset of patients with adverse prognostic features (PSA > 10 ng/mL at diagnosis) derived the greatest benefit at a dose of 78 Gy compared to 70 Gy, in terms of biochemical and clinical failure [26]. Furthermore, with increasing doses, accurate and precise delivery of radiation using technology such as image-guided radiation therapy (IGRT) becomes even more important to avoid normal tissue toxicities. IGRT should also be considered in order to compensate for changes in target volume as the tumor shrinks.

Recently, both volumetric-modulated arc therapy (VMAT) and helical tomotherapy techniques have been evaluated as novel ways to deliver radiotherapy. Several preliminary studies have evaluated the dosimetric feasibility of treating a broad spectrum of prostate cancer with VMAT, including localized, locally advanced and postoperative disease [27, 28]. A retrospective review of 292 patients treated with a VMAT method to a dose of 77.4 Gy was compared to a fixed-angle, 7-field IMRT technique using the same planning datasets and contours. It was reported that VMAT therapy resulted in a lower dose of delivery to critical structures such as the penile bulb, bladder, and femoral heads, particularly in high-dose regions with comparable dose delivery to target volumes when compared to IMRT. These results suggest further evaluation of VMAT in order to reduce radiotherapy-related acute and chronic toxicities [29]. Similar dosimetric studies evaluating the ability of helical tomotherapy to improve dose conformity and normal tissue sparing in comparison to IMRT have demonstrated overall improvement in critical organ sparing as well as achieving better homogeneity of dose delivery [30]. Of note, the improving precision and dose escalation in the administration of radiotherapy to target volumes has lead to the development of simultaneous integrated boost radiotherapy, which delivers different doses per fraction to different target regions of interest. Consequently, whole pelvis radiation therapy, which has traditionally been a controversial issue, is now a valid therapeutic consideration for node-positive or high-risk patients because high doses can be delivered to a focal target volume while also administering a lower dose of RT to the rest of the pelvis which may promote locoregional control and address micrometastatic disease [31].

*3.2. Androgen Deprivation Therapy (ADT) in Combination with Radiotherapy.* Arguably, combination therapy with radiation and long-term androgen deprivation therapy

(ADT) has been one of the most important modifications to modern clinical practice for prostate cancer. The rationale of the combined approach is that the addition of ADT is believed to slow progression of the tumor by eliminating the hormonal stimulus that drives cancer cell proliferation [32]. Furthermore, in vivo animal models have shown that the combined effect of ADT and radiotherapy increases overall cell kill and diminishes growth velocity of the surviving cancer cells [33, 34]. Several agents, such as luteinizing hormone-releasing hormone (LHRH) analogs and nonsteroidal antiandrogens have been used to exploit the sensitivity of prostate cancer to hormonal suppression. Of note, surgical (bilateral orchiectomy) and medical castration are of equal efficacy and using multiple methods of androgen blockade does not confer an additive benefit for nonmetastatic patients [35].

Several prospective studies have demonstrated that the combination of radiotherapy and long-term androgen suppression improves disease control and survival, compared with either treatment alone for men with adverse risk factors. A prospective phase III trial, EORTC 22863, enrolled 415 men randomized to either radiotherapy alone or radiotherapy plus three years of LHRH analog (goserelin) to assess the additive effect long-term ADT in locally advanced patients. The study reported an increase in both disease-free and overall survival in the combination therapy group. Furthermore, the 10-year results of this study found no increase in cardiovascular toxicity in addition to the survival benefit [36–38]. In 2009, a prospective randomized study by Widmark et al. involving 875 high-risk patients (stage T3, PSA < 70 ng/mL) receiving ADT monotherapy (total androgen blockade for 3 months followed by continuous flutamide 250 mg) or ADT with radiotherapy also demonstrated a survival benefit with a minimal yet acceptable increase in side effects in the combination therapy cohort [39]. Similar findings were reported by D'Amico et al. in 2008, who reported an overall survival benefit in high-risk patients receiving combination therapy, despite a shorter course of ADT treatment than the aforementioned studies [40].

The optimal duration of ADT has been a controversial topic, and several studies have examined whether or not the long-term side effects of ADT outweigh the clinical benefits. It is understood that the incidence of side effects correlates with the duration of ADT treatment. Long-term complications associated with ADT are both real and severe, ranging from osteoporosis with risk of pathologic fracture, metabolic dysfunction including development of diabetes as well as cardiovascular disease with potential for fatal myocardial infarction [41, 42]. In 2009, Bolla et al. reported the results of the prospective EORTC 22961 trial randomizing 885 men with T2c-T4, N0 disease, in order to assess whether short-term ADT (6 months) was able to achieve the same survival benefits that had previously been reported with long-term ADT (≥2 years) while simultaneously reducing exposure to hormonal therapy. The 5-year overall mortality rate was 19.0% and 15.2% for short-term and long-term ADT, respectively; demonstrating that short-term ADT in conjunction with radiotherapy is inferior with regards to overall survival [43]. Furthermore, RTOG 9202, a large phase III trial of 1554 patients with T2c-T4 non-metastatic high-risk disease, reported that long-term ADT with radiotherapy is superior to short-term ADT with regards to disease-free survival, risk of distant metastasis, local progression and incidence of biochemical failure; however, no difference in overall survival was observed. A criticism of this study by Horwitz and colleagues is that it was not sufficiently powered to assess for overall survival. Upon subset analysis of 337 patients with a Gleason score 8–10 a benefit in overall survival was seen in the long-term ADT cohort [44]. A Canadian multicenter phase III trial examining short-versus long-term neoadjuvant ADT in combination with radiotherapy found that increasing the duration of neoadjuvant ADT from 3 to 8 months conferred a significant disease-free survival benefit among high-risk patients (42% versus 71% 5-year disease-free survival rate) [45]. While the duration of ADT has definitively demonstrated an effect on patient survival, the sequencing (adjuvant, concurrent, neoadjuvant) of when ADT is administered in relation to radiotherapy does not appear to affect outcomes in men with high-risk prostate cancer [46–48].

In summary, the current standard of care for high-risk and locally advanced disease is EBRT in conjunction with long-term ADT; specifically, a 3D-CRT or IMRT radiation therapy technique to a dose of 75–80 Gy in conjunction with long-term ADT in a neoadjuvant, concurrent, or adjuvant setting for approximately 2-3 years. Generally, high-risk patients are usually not considered for treatment with brachytherapy; however, certain clinical scenarios may warrant the use of brachytherapy boost in combination with EBRT, with consideration of short-term ADT [49]. Additionally, a surgical approach may be considered for selected high-risk-patients, although, it is a seemingly less popular approach due to the invasive nature in comparison to EBRT as well as the distinct set of complications which surgery poses; including perioperative mortality, long-term sexual dysfunction, and urinary incontinence. Additionally, the high likelihood that postoperative radiotherapy will be required potentially exposes patients to toxicities of both surgery and radiotherapy.

*3.3. Surgery as a Treatment Option for High-Risk Prostate Cancer.* Like radiotherapy, as technology (i.e., laparoscopic, robotic) continues to improve, some of the issues with surgical management for high-risk patients are no longer valid. For example, with the advent of robotic surgery some experienced urologists now consider stage T3a prostate cancer as an operable disease. Men with clinically localized tumors without fixation that can be completely excised may be candidates for radical prostatectomy (RP) with pelvic lymph node dissection if they have a reasonable life expectancy. Lau et al., reported a post-RP overall survival of 67% at 10 years among patients with adverse prognostic features (Gleason score ≥ 8), suggesting that radical prostatectomy may be a viable alternative for patients who are not candidates for radiotherapy or whom prefer surgery [50].

Additionally, two recent studies have shown that surgical intervention in the high-risk cohort may result in superior

clinical and survival outcomes. A 2010 retrospective study by Zelefsky et al., reported that high-risk patients undergoing RP had a lower risk of metastatic progression and PCSM compared to patients receiving IMRT (≥81 Gy) [51]. High-risk disease was defined as clinical stage T3, Gleason score 8–10, or PSA > 20 ng/mL; within this subgroup those patients treated with RP with bilateral lymphadenectomy had a 7.8% decrease in 8-year metastatic progression compared to those treated with RT (hazard ratio, 0.35). Furthermore, a 2010 retrospective analysis by Abdollah et al. examined survival outcomes patients treated with RP, RT, or observation between 1988 and 2006 and noted favorable survival rates in most patients undergoing RP [52]. Amongst high-risk patients (T2c and/or Gleason score 8–10), patients ≤ 69 years of age treated with RP derived the greatest survival benefit (PCSM 5.8–7.2%) in comparison to those treated with RT or observed (PCSM 9.9–11.3% and 21.5–21.9%, resp.). However, among patients older than 70 years of age, treatment with RT was associated with a lower PCSM (12.2–21.1%) when compared to those treated with RP or observation (PCSM = 12.2–21.1%, 18.5–19.8%, resp.).

A significant number of patients will still require post-operative radiotherapy following radical prostatectomy for certain pathologic high-risk features. Recently, three separate studies have demonstrated that adjuvant radiotherapy following radical prostatectomy improves disease control (biochemical progression-free survival), and Thompson et al. reported a marked overall survival benefit for high-risk patients following radical prostatectomy [53–56]. Furthermore, aforementioned studies by Spahn et al. and Walz et al. have documented that men with high-risk disease do not have uniformly poor outcomes after undergoing radical prostatectomy. Indeed, there is a subset of patients within this risk group that derive a comparative benefit from surgery, and thus RP should remain a genuine consideration for therapeutic intervention [11, 12, 57].

## 4. Chemotherapy and Prostate Cancer

*4.1. The Use of Chemotherapy in Castration-Refractory Prostate Cancer.* Although long-term ADT plus radiotherapy is currently the standard care for high-risk patients, many high-risk prostate malignancies still recur. Importantly, a proportion of these high-risk prostate tumors will become refractory to hormonal therapies which place the patient at risk of developing recurrent or metastatic disease [36, 58, 59]. Strategies to enhance the therapeutic benefits of treatment and improve survival outcomes have been studied, with a particular emphasis on systemic treatment such as chemotherapy. Castration-refractory metastatic prostate cancer patients were the first group of patients in which the efficacy of chemotherapy was assessed. The CALBG 9182 study examined a combination of mitoxantrone and hydrocortisone versus hydrocortisone alone. While there was no survival benefit reported among the 242 men with castration-refractory disease, a delay in disease progression and time to treatment failure was observed. Additionally, this study also confirmed the palliative benefits of this regimen previously reported in a small randomized trial in Canada [60, 61]. The CALBG 9182 study generated interest in exploring other chemotherapeutic agents in this population.

Two prospective phase III trials for men with metastatic castration-refractory prostate cancer helped to establish docetaxel and prednisone as the preferred chemotherapy regimen. SWOG 9916, a prospective trial randomizing 674 men with castration-refractory disease, compared survival outcomes and toxicity profiles in a head-to-head comparison of a docetaxel plus estramustine versus mitoxantrone. The docetaxel-containing regimen demonstrated a significant increase in overall survival of nearly two months; however, there was also an increase in side effects, including neutropenic fever and cardiovascular events [62]. Subsequently, it has been reported that the addition of estramustine to docetaxel has been shown to increase side effects without enhancing efficiency [63]. The second pivotal study was the TAX 327 trial which compared docetaxel and mitoxantrone; prednisone was also administered in both regimens. Importantly, estramustine was not a component of the docetaxel-containing regimens and docetaxel was given in a weekly or in an every three-week schedule. Patients in the docetaxel every three-week arm demonstrated an improved median survival of 2.5 months with a 24% reduction in risk of death [64]. The 10-year update of this study reported continued survival benefit in the docetaxel every three-week arm [65].

*4.2. The Role for Chemotherapy in the Management of High-Risk Localized Disease.* These studies in metastatic castration-refractory patients helped lay the groundwork for early use of docetaxel and other agents as part of the primary treatment for high-risk and locally advanced prostate cancer patients (Table 4). The rationale of using chemotherapy and other systemic agents in the adjuvant setting is that micrometastatic disease as well as androgen-resistant clones will encounter cytotoxic treatment earlier [17]. As radiotherapy techniques permit increasing dose escalation, chemotherapy can play a more important synergistic role by radiosensitizing tumor cells at the primary site while also addressing micrometastatic disease. Specifically, docetaxel, a radiosensitizing cytotoxic antimicrotubule agent has been used extensively in the treatment of breast, ovarian, and nonsmall-cell lung cancer [66–68]. It exerts a direct cytotoxic effect by arresting cells in M phase, thereby preventing cell division. Furthermore, by stabilizing the cells in M phase, a radiosensitive phase of the cell cycle, docetaxel is able to synergize the effect of radiation [69–71].

A critical phase III multicenter study by Rosenthal et al. highlighted the severe toxicities that may occur with multichemotherapy multimodal regimens. A total of 397 high-risk non-metastatic patients (PSA 20–100 ng/mL and Gleason score ≥ 7 or stage ≥ T2, Gleason score 8 and PSA < 100 ng/mL) enrolled in RTOG 99-02 and were randomized to an ADT plus radiotherapy with four cycles of adjuvant paclitaxel, estramustine and oral etoposide (TEE) group, or an ADT plus radiotherapy alone group. After opening in 2000, the trial was closed after 4 years due to excess thromboembolic events and severe toxicities, particularly in the adjuvant chemotherapy arm. With regards to short-term toxicities, 71% (136/192) of patients in the adjuvant TEE plus

Table 4: Summary of randomized control trials involving chemotherapy for high-risk localized prostate cancer.

| Study (reference) | Chemo sequencing | Chemo regimen | Study arms | Number of patients | High-risk criteria | | |
|---|---|---|---|---|---|---|---|
| | | | | | Stage | Gleason | PSA |
| RTOG 9902 [14] | Adjuvant | paclitaxel estramustinee toposide (TEE) | ADT + RT versus ADT + RT + TEE | 397 | any T | ≥7 | 20–100 |
| | | | | | ≥ T2 | 8–10 | <100 |
| RTOG 0521 [15] | Adjuvant | Docetaxel | ADT + RT versus ADT + RT + docetaxel | 612 | any T | ≥9 | ≤150 |
| | | | | | ≥ T2 | 8 | <20 |
| | | | | | any T | 7-8 | ≥20–150 |
| Kumar et al. [72] | Concurrent | Docetaxel | RT + docetaxel | 22 | T3-T4 | | |
| | | | | | T1b-T2 | ≥8 | |
| | | | | | T1c-T2 | 5–7 | ≥10 |
| AGUSG 03-10 [73] | Concurrent | Docetaxel | RT + docetaxel +/− ADT | 20 | ≥T3 | 8–10 | |
| | | | | | | 7 | >10 |
| Sanfilippo et al. [74] | Concurrent | Paclitaxel | ADT + RT versus ADT + RT + paclitaxel | 22 | TxN1 | >7 | >10 |
| Hussain et al. [75] | Neoadjuvant | Docetaxel estramustine | docetaxel, EMP +/− RP, RT | 21 | ≥T2b | 8–10 | ≥15 |
| Hirano et al. [76] | Neoadjuvant/ concurrent | Estramustine | ADT + RT versus ADT + RT + EMP | 39 | ≥T3 | 8–10 | >20 |
| SWOG S9921 [77, 78] | Neoadjuvant | Mitoxantrone | RP + ADT versus RP + ADT + MTX | 983 | pT3b-T4 | ≥8 | |
| | | | | | | 7 | >15 |
| CALGB 90203 [79] | Neoadjuvant | Estramustine docetaxel | RP versus EMP and docetaxel + RP | recruiting | T1-T3a, NX, M0 | | |

ADT: androgen deprivation therapy; RT: radiotherapy; TEE: paclitaxel, estramustine, etoposide; EMP: estramustine phosphate; RP: radical prostatectomy; MTX: mitoxantrone.

ADT and radiotherapy cohort reported grade 3 or greater toxicities compared with only 37% in the radiotherapy and ADT cohort. There was a significant increase in hematologic and gastrointestinal toxicity but not genitourinary toxicity. Furthermore, in terms of long-term complications, three cases of myelodysplasia/acute myelogenous leukemia were noted [14]. A follow-up prospective phase III trial, RTOG 05-21, was designed to assess the efficacy of a less toxic adjuvant chemotherapy regimen when combined with ADT and radiotherapy. This ongoing study compares high-risk patients receiving ADT (LHRH agonist and oral antiandrogen) and radiation (3D-CRT or IMRT) with or without adjuvant docetaxel chemotherapy. Enrollment criteria consists of: (1) Gleason score ≥ 9, PSA ≤ 150 ng/mL and any T stage disease (2) Gleason score 8, PSA < 20 ng/mL, stage T2 disease or higher (3) Gleason score 7-8, PSA 20–150 ng/mL, any T stage [15]. The results of this trial will certainly help to elucidate the role of chemotherapy in the adjuvant setting for high-risk patients.

Kumar et al. conducted a phase I trial of concurrent weekly docetaxel with 3D-CRT in order to discern to maximal tolerated dose (MTD) of weekly docetaxel for patients with unfavorable localized prostate cancer. The 22 patients who were enrolled in the concurrent docetaxel and 3D-CRT regimen met inclusion criteria of: (1) T3-T4 disease (2) T1b-T2 disease and Gleason score ≥ 8 or (3) T1c-T2 disease with Gleason score 5–7 and PSA ≥ 10. The MTD of weekly docetaxel was determined to be 20 mg/m$^2$ in conjunction with 3D-CRT, in general, this regimen was considered to be well tolerated without any excessive or objectionable toxicity. Other relevant findings from the study include the side effect of grade 3 diarrhea which was the dose-limiting toxicity; however, no hematologic adverse side effects were noted [72]. Another small phase I study involving concurrent docetaxel and radiotherapy supported Kumar's findings of permissible toxicity with radiosensitizing regimens. The AGUSG 03-10 phase I/II prospective trial was a continuation upon Kumar et al.'s earlier work with docetaxel and 3D-CRT. In this study, concurrent IMRT was given with the previously determined MTD of weekly docetaxel at 20 mg/m$^2$. Twenty high-risk patients with at least stage T3 disease, a Gleason score of 8–10 and PSA > 10 ng/mL were enrolled on this concurrent chemoradiation protocol. In general, the concurrent IMRT with weekly docetaxel regimen was well tolerated with acceptable toxicity. Furthermore, 85% of the patients were free of biochemical disease recurrence at a mean followup of 11.7 months. Of note, there were no grade 3 or 4 toxicities reported and the most common toxicities were grade 2 fatigue (40%), grade 2 diarrhea (40%), and grade 2 urinary frequency (35%) [73]. The two aforementioned studies highlighted the emerging role that concurrent taxane-based chemotherapy may play in the management of high-risk prostate cancer.

Sanfilippo et al. conducted a prospective phase I/II study of biweekly paclitaxel and concurrent radiotherapy in order to determine the maximum tolerated dose of paclitaxel in androgen-ablated locally advanced prostate cancer. Paclitaxel, a taxane molecule, has a similar mechanism of action

to docetaxel which leads to the accumulation of cells in G2/M phase having both cytotoxic as well as radiosensitizing effects [80, 81]. This study involved 22 patients who had T2–T4 tumors with Gleason scores > 7 and/or PSA levels > 10 ng/mL and/or pathologic staging of TxN1. Patients underwent 3D-CRT with doses ranging from 63–73.8 Gy. It was concluded that concurrent biweekly paclitaxel with 3D-CRT is feasible with an MTD for combined paclitaxel and 3D-CRT of 73.8 Gy. Four patients developed grade 3 diarrhea, three at a dose of 66.6 Gy and one at the MTD of 73.8 Gy. With regards to patient outcomes, 21 of 22 patients (95%) were still alive and 6 of 22 (27%) patients experienced biochemically recurrent disease at a median followup of 28 months [74]. Importantly, in comparison to the aforementioned studies involving concurrent radiotherapy with paclitaxel, patients in this trial also received ADT in addition to concurrent chemoradiotherapy and the toxicities were not prohibitive.

Examining the efficacy of chemotherapy in the neoadjuvant setting in combination with ADT and radiotherapy is becoming an area of increasing interest. Hussain et al. evaluated the safety of neoadjuvant docetaxel and estramustine chemotherapy alone in 21 patients with high-risk cancer defined as clinical stage T2b or greater, PSA > 15 ng/mL and/or a Gleason score of 8–10. Induction chemotherapy with docetaxel and estramustine was reported to be a well-tolerated and a feasible regimen for the high-risk cohort. Patients did experience grade 3 and 4 toxicities in the form of neutropenia in nine patients and deep vein thrombosis in two patients. Furthermore, the efficacy of this regimen in comparison to ADT remains unclear and its use in conjunction with other modalities was not evaluated [75]. However, a prospective randomized study in Japan assessed the safety and efficacy of neoadjuvant ADT plus estramustine phosphate (EMP) combined with 3D-CRT for patients with both intermediate and high-risk prostate cancer. A total of 39 patients were randomized into a neoadjuvant ADT alone group or neoadjuvant ADT with EMP group, both groups received 3D-CRT to a total dose of 70 Gy. The 4-year biochemical relapse-free survival was 61% in the group receiving combined chemotherapy and androgen ablation compared to the 49% in the group receiving only neoadjuvant ADT. Additionally, there were no severe toxicities reported leading the authors to conclude that the combination of ADT with EMP in the neoadjuvant setting appears to be better than neoadjuvant ADT alone. However, both regimens were unable to prevent biochemical failure and thus suggested additional adjuvant therapy, particularly, in the high-risk cohort with pretreatment PSA > 20 ng/mL [76].

Recently, the role of chemotherapy in conjunction with radical prostatectomy has also been examined. Similarly to RTOG 99-02, which has halted due to prohibitive toxicities, SWOG 9921, a randomized phase III trial, prematurely closed the chemotherapy plus ADT arm due to the development of acute myelogenous leukemias. In this study, 983 patients with high-risk features were randomized to receive adjuvant ADT with or without mitoxantrone in the postradical prostatectomy setting. This study underlined the importance of prospective trials to assess potential safety issues for patients. In this particular case, the risk of secondary malignancies associated with a mitoxantrone-containing adjuvant chemotherapy regimen was an unexpected problem [77]. Importantly, in 2011 Dorff et al. reported preliminary data from the SWOG S9921 study because of the potential implications for future prospective trial design. Among the 481 high-risk patients (Gleason ≥ 8, preoperative PSA > 15 ng/mL or both) receiving ADT-alone after RP, the estimated 5-year biochemical failure-free survival is 92.5% and the 5-year overall survival is 95.9%. In light of the favorable outcomes achieved with adjuvant ADT post-RP, this study highlights the difficulty in demonstrating that the addition of chemotherapy can improve upon currently available therapies given the extremely low rate of disease recurrence and PCSM [78]. Of note, the cancer and leukemia group B has initiated an ongoing phase III trial (CALGB 90203) in high-risk patients randomizing them to be treated with neoadjuvant estramustine and docetaxel followed by surgery or surgery alone [79].

## 5. New Approaches on the Horizon

The need to improve high-risk disease management has prompted the development of novel agents, several of which may be genuine contenders to impact disease outcomes in the future. Initial studies in castration-refractory disease have been useful in order to characterize the efficacy and safety of these potential therapeutic agents.

Sipuleucel-T (APC8015), a cancer vaccine, is an active cellular immunotherapy that stimulates a prostate cancer-specific T-cell immune response against prostatic acid phosphatase (PAP), an antigen expressed by approximately 95% of prostate cancer cells [82–84]. Specifically, autologous antigen-presenting cells (APCs) collected via leukapheresis undergo ex vivo stimulation with PA2024 (recombinant fusion protein of PAP and GM-CSF) and are subsequently infused into the patient to exert an immunogenic effect. Presumably, the interaction of T cells with the PA2024-activated APCs primes the T cells for their highly specific tumoricidal activity [85, 86]. A 2010 multicenter double-blind, placebo-controlled study by Kantoff et al. evaluated a total of 512 patients with metastatic castration resistant disease in order to compare the efficacy of sipuleucel-T to placebo. Sipuleucel-T was shown to prolong overall survival with a 22% relative reduction in risk of death (hazard ratio, 0.78) which prolonged median survival by 4.1 months, however, no change in the time to disease progression was noted. There were no excessive toxicities observed, however, an increase in chills, fever, and headache was associated with infusion of sipuleucel-T [87]. Sipuleucel-T was approved by the FDA in April 2010 for the treatment of asymptomatic or minimally symptomatic metastatic castration-refractory prostate cancer. The early findings with sipuleucel-T appear to be promising but its efficacy in conjunction with chemotherapy and potential use in earlier settings such as high-risk prostate cancer is yet to be determined.

While prostate cancer patients often initially derive benefit from ADT, a proportion of these patients will

develop castration-refractory prostate cancer characterized by progression of disease despite castrate levels of circulating testosterone. The persistence of ligand-mediated androgen receptor signaling implicates extragonadal (prostate, adrenal, intratumoral) androgen production as a potential mechanism of resistance to ADT rather than an androgen-independent mechanism. Abiraterone acetate suppresses extragonadal androgen biosynthesis via inhibition of CYP17 (cytochrome P-450c17), an enzyme that has been shown to be over expressed in castration-refractory disease. In a recent 2011 phase III multicenter trial, de Bono and colleagues evaluated the efficacy of abiraterone in castration-refractory patients with progression after docetaxel treatment. Patients were randomized to receive prednisone with either abiraterone or placebo and there was a median follow-up time of 12.8 months among the 1195 enrolled patients. A clear survival benefit was reported in the abiraterone-prednisone group, with a 35.4% reduction in the risk of death compared to the placebo cohort (hazard ratio, 0.65) which translated into an increase in overall survival of 3.9 months (14.8 versus 13.9 months). Secondary end points including PSA progression, progression-free survival and PSA response rate also favored the patients whom received abiraterone. Of note, while both treatment cohorts received prednisone as part of the treatment regimen, steroid-related toxicities and side effects were more frequent among patients receiving the androgen biosynthesis inhibitor. However, the general consensus regarding this study is that abiraterone acetate plus prednisone is effective in prolonging overall survival with minimal increase in additional toxicities for patients with metastatic castration-refractory prostate cancer with progression after chemotherapy [88, 89].

A new therapy, MDV3100, targets androgen receptor-mediated treatment resistance with a distinct mechanism of action to that of abiraterone. While the concept of androgen-receptor antagonism is not a novel concept, MDV3100 is notable for its extremely high receptor-binding affinity, ability to induce tumor cell apoptosis and pure androgen receptor antagonism [90]. These characteristics ensure more effective androgen signaling blockade in comparison to other agents such as bicalutamide that have a relatively lower receptor binding affinity and may exhibit partial agonism at the androgen receptor; a potential cause of refractory disease. Although, this agent is not as far along as sipuleucel-T and abiraterone in terms of clinical testing, a phase 1-2 study by Scher et al. has generated cautious optimism regarding MDV3100. This multicenter dose-escalation trial enrolled 140 patients with progression metastatic castration-refractory disease in order to assess the safety and tolerability of MDV3100 as well as to establish the maximum tolerated dose. The maximum tolerated dose was determined to be 240 mg/day and the most predominant grade 3-4 treatment-related toxicity was dose-dependent fatigue. Of note, antitumor effects were appreciated at all doses. This study has helped to corroborate that persistent androgen-receptor signaling is veritable target for castration-refractory disease and further preclinical and clinical studies are need to decided whether MDV3100 can truly impact outcomes among prostate cancer patients [91].

## 6. Conclusion

While considerable progress has been made in the treatment of high-risk prostate cancer, there is a clear need to continue prospective randomized clinical trials in order to optimize treatments. Combination therapies involving radiotherapy, androgen deprivation therapy, surgery and chemotherapy have yielded varied success. Importantly, the combination of long-term ADT and radiotherapy and has been particularly successful and chemotherapy may have the potential further improve outcomes. As we continue to appreciate the additive and synergistic effects of multimodality therapy, we must also acknowledge the potential for additive toxicities.

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*Review Article*

# Modern Detection of Prostate Cancer's Bone Metastasis: Is the Bone Scan Era Over?

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Prostate cancer cells have an exquisite tropism for bone, which clinically translates into the highest rate of bone metastases amongst male cancers. Although in the latest years there has been an active development of new "bone targeted" therapies, modern diagnostic techniques for bone metastases still relies mostly on $^{99m}$Tc bone scanning (BS) and plain X-ray. BS dramatically lacks specificity and sensitivity. Recent publications using modern imaging technologies have clearly pinpointed that BS grossly underestimates the true prevalence of bone metastasis. In addition BS does not allow tumour measurement and is, therefore, not appropriate to monitor response to therapy. This might be extremely important in patients harbouring high-risk localized disease that are eventually candidate for local therapy. Here we reviewed what are the emerging imaging strategies that are likely to supplant BS and to what extent they can be used in the clinic already.

## 1. Introduction

In men over the age of 50, prostate cancer (PCa) is the most commonly diagnosed cancer and the second leading cause of death by cancer [1]. With the intense use of PSA testing, most PCa are diagnosed at an early stage, and most are candidate to intent-to-cure therapies such as radical prostatectomy, external beam radiation therapy, or seeds implant. Initially essentially intended for low- or intermediate-risk disease, local therapies are now more often indicated in patients with high-risk localized disease and locally advanced disease. Indeed, hormone therapy has failed to demonstrate to increase overall survival when it was not associated with a local treatment [2]. In that high-risk population; however, it is critical to precisely rule out the presence of metastases since as for today it still represents the tipping point for excluding local control.

PCa cells spreading out of the prostate show an exquisite tropism for bone. In most patients, the initial seeding of metastatic deposits occurs in the hematopoietic red marrow of the axial skeleton leading to the formation of bone metastases (BMs). BMs represent the initial and the main metastatic site in about 80% of PCa patients, therefore, being one of the most important prognostic factors [3, 4]. Skeletal complications, most commonly designed as "skeletal-related events (SREs)," account for most of the PCa's morbidity and mortality [5]. Replacement of hematopoietic tissues in the bone marrow by PCa cells leads to anaemia while abnormal tissue growing in the bone marrow can lead to pain, fractures, and spinal cord compression. As for today, despite the development of bone-targeted strategies, BMs are still considered incurable [6].

The main phenotypic manifestations of PCa BMs are their tropism to the axial skeleton (skull, vertebra, ribs and collar bone, scapula, and proximal femur) and their most often osteoblastic appearance, resulting from the stimulation of osteoblasts [6]. BM, are often associated with increased levels of serum markers of osteoblastic proliferation, such as bone-specific alkaline phosphatase [7].

Interestingly, there has been no major evolution in the diagnostic algorithm for BM in the recent years. Most international guidelines still recognized $^{99m}$Tc bone scintigraphy (BS) and plain X-ray radiography as the cornerstone diagnostic techniques to detect and follow BM [8, 9].

Most modern clinical trials still incorporate BS as a major component to define time to progression, although it is recognized as not appropriate to measure tumour response and required serial examinations to define progression [10–12]. There are, however, several technological developments addressing this important diagnostic aspect. Here we will review some of these developments.

## 2. Why and When Bone Imaging Is Required?

Early BM detection is critical in the management of patients with high-risk PCa. Newly diagnosed patients with localized disease and no metastases may benefit from radical treatment with curative intent. In contrast, most guidelines recognize that patients with BM should be kept away from local therapy to avoid unnecessary side effects and treated with systemic therapy [9]. With modern PSA-based diagnostic strategies, many patients are diagnosed while they are still asymptomatic. In screening trials, BMs are detected at diagnosis in less than 10% of the patients [13]. This means that there is no need to perform an initial BS in every new patient. PSA value and Gleason's score at diagnostic remain the strongest BM's indicators. In a study conducted on 60 patients with newly diagnosed PCa, Rana et al. demonstrated that the positive predictive value of a PSA >100 ng/mL was 100% [14]. Together with PSA, $cT_{3-4}$ stage and a Gleason score >7 are the other predictors of BM; their positive predictive value being, respectively, 71.4% and 81% [14]. Based on this trial and others, the EAU guidelines recommend that [...] *a staging bone scan may be superfluous if the serum PSA concentration is less than 20 ng/mL in asymptomatic patients with well-, or moderately differentiated tumours. In contrast, in patients with poorly differentiated tumours and locally advanced disease, a staging bone scan should be obtained irrespective of the serum PSA value* [...] [9]. Briganti et al. have developed a risk stratification tool to select patients requiring initial imaging from a series of 853 consecutive patients [15]. Their classification and regression tree (CART) stratifies patients into low risk (biopsy Gleason ≤7, $cT_{1-3}$, and PSA <10 ng/mL), intermediate risk (biopsy Gleason ≤7, $cT_{2-3}$, and PSA >10 ng/mL), and high risk (biopsy Gleason >7) conferring a risk of BM of 1.8%, 8.5%, and 16.4%. Briganti's regression tree shows higher sensitivity (87.5%) compared to the EAU, AUA, and NCCN guidelines [8, 9, 16].

Later in the course of the disease, BM detection may be discussed in case of PSA recurrence after radical treatment or when the tumour becomes resistant to castration (CRCP). This information may be important to guide initiation of hormone therapy, chemotherapy, or bone-targeted agents. Gomez et al. have evaluated the use of BS in 153 patients presenting with a PSA recurrence after radical prostatectomy. This study demonstrated that it is unlikely to have a positive BS in patients with a serum PSA of <7 ng/mL except in case of skeletal symptoms [17]. Pound et al. have reviewed a large series of radical prostatectomy performed at the Johns Hopkins University and identified 304 patients with a subsequent PSA rise [18]. The median actuarial time to metastases was 8 years from the time of PSA level elevation. In survival analysis, time to biochemical progression ≤2 years ($P < 0.001$), Gleason's score ≤8 ($P < 0.001$), and PSA doubling time ≤10 months (PSADT) ($P < 0.001$) were predictive of the probability and time to the development of metastatic disease. Choueiri et al. have reviewed case notes of 292 patients from CaPSURE who had recurrence and had undergone at least 1 imaging study (BS, computerized tomography (CT), or magnetic resonance imaging (MRI) of the abdomen and the pelvis) [19]. Overall only 11% patients showed a positive imaging study, and this was unlikely to occur when PSA was ≤5 ng/mL or PSADT ≥10 months [19].

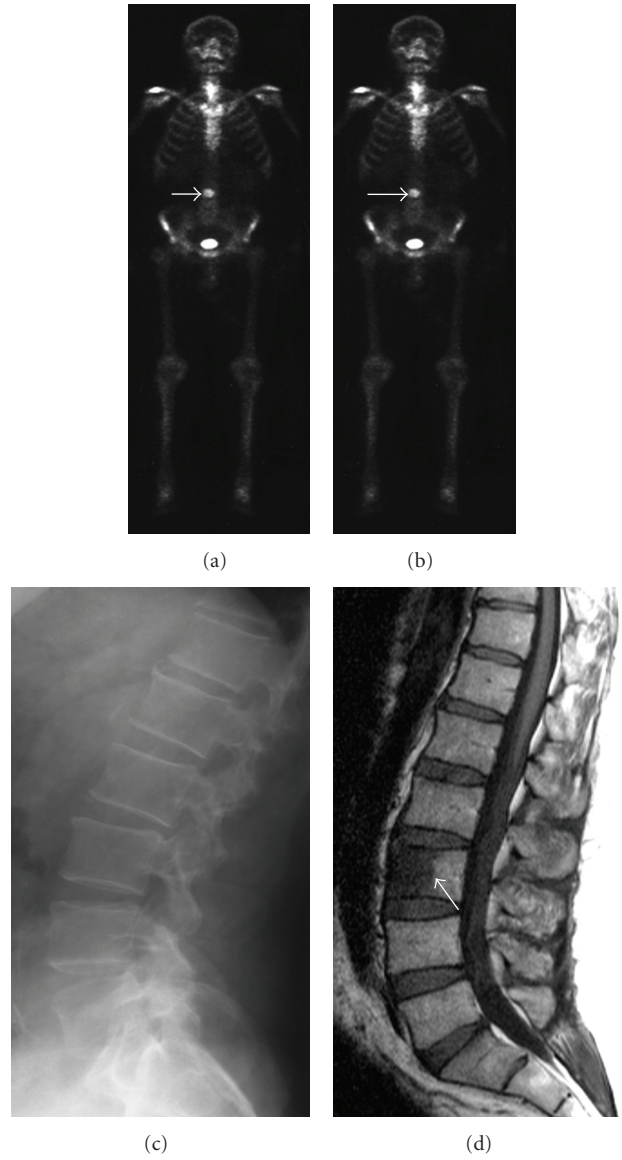


Figure 1: Example of a 55 years old patient diagnosed with high-risk localized disease. $^{99m}$Tc bone scan shows an area of uptake in the body of the 3rd lumbar vertebra ((a) and (b)). Confirmatory X-ray is read as normal (c) although MRI of the axial skeleton (T1 sequence, (d)) shows a large focal area of malignant replacement of the bone marrow.

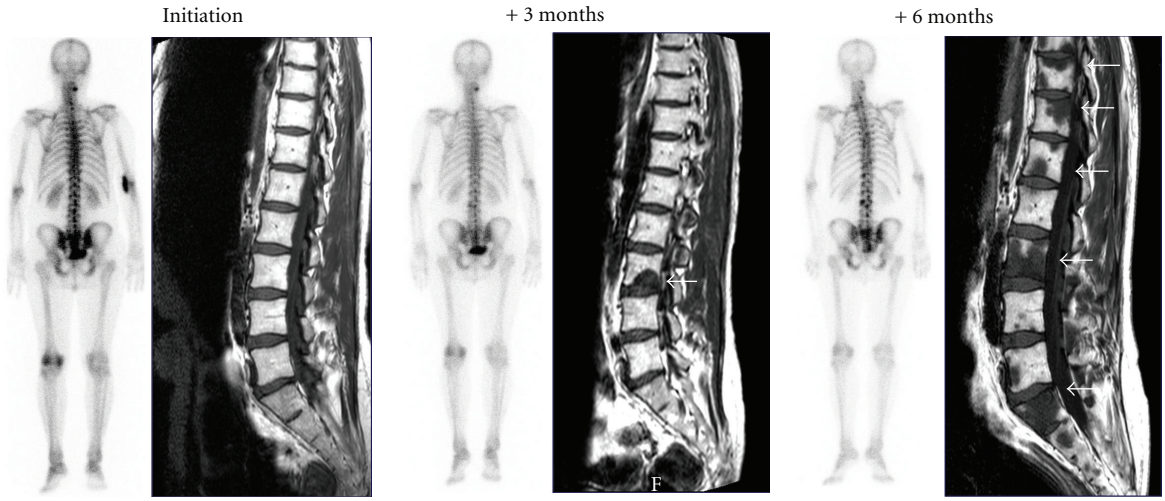


Figure 2: Consecutive series of three $^{99m}$Tc bone scans (BS) and MRI acquired three months apart on a patient included in a clinical trial designed for M0 CRPC. Only the third BS is adjudicated as positive by the central review although he was already progressive on MRI at the second metastatic workup.

Smith et al. have reported the natural history of 201 non-metastatic (M0) CRCP patients consisting of the placebo group of an aborted trial with zoledronic acid [20]. At 2 years, only 33% of patients had developed BM. A baseline PSA level >10 ng/mL and a high PSA velocity independently predicted shorter time to first BM. Patients with a PSADT <6 months were those most likely to rapidly develop BM. More recently, Smith et al. have reported the natural history of placebo group of another M0 CRCP study conducted with the endothelin receptor A inhibitor, atrasentan [21]. Patients included in the atrasentan trial had a shorter PSADT (mean ± SD: 5.9 ± 3.62 months) than those in the zoledronic acid trial (mean ± SD: 9.7 ± 4.7 months) [20, 21]. In multivariate analyses, a baseline PSA ≥13.1 ng/mL was associated with shorter time to the first BM and BM-free survival.

In conclusion, all these data pinpoint at a high Gleason's score, a high PSA, and a short PSADT being important to decide which patients should receive bone investigation to search for BM. Taken together, these data should help the clinician schedule follow-up examination.

*2.1. $^{99m}$Technetium ($^{99m}$Tc) Bone Scintigraphy.* Today, standard diagnostic algorithms of bone metastases still rely primarily on $^{99m}$Tc methylene diphosphonate (MDP) bone scintigraphy (BS). BS has been used for decades as the first-line modality for the screening of PCa bone metastases [22, 23]. $^{99m}$Tc-MDP is a nonspecific marker of osteoblastic activity. Studies using microautoradiography have demonstrated that $^{99m}$Tc-MDP localizes along mineralization fronts. The isotope is occasionally found in the substance of the osteoid but is absent from the cytoplasm and nuclei of osteoblasts and osteocytes [24]. $^{99m}$Tc-MDP accumulates in response not only to tumour but also to degenerative joint disease, benign fractures, and inflammation [25–27]. Therefore, BS detects bone metastases at an advanced stage of tumour infiltration, when osteoblastic reaction to metastatic cell deposit has occurred [28]. Sensitivities reported in the literature range between 62 and 89% and, therefore, could be considered acceptable [28]. BS's main problem is its low specificity so that its diagnostic effectiveness has been widely questioned in the literature [29, 30]. Indeed, in many cases, regions of increased uptake cannot be definitively characterized negative or positive for malignancy. Routinely, it will end up in reading characterized as "equivocal," "possible," "suspicious," "likely," "highly suspicious," "almost certain," a series of definition encompassing all cases in which imaging findings could not be categorized confidently as metastatic or benign, regardless of the level of incertitude. Usually equivocal BS uptakes will be characterized by targeted X-ray to distinguish benign (fracture, Paget's, degenerative joint disease, etc.) from malignant (metastatic) origin [31]. This association is imperfect, and the diagnosis may remain equivocal after this workup. In clinical practice, a normal bone radiograph associated with an abnormal scan is highly suggestive of BM [32]. But this conclusion invokes conventional wisdom or suggestion more than it relies on a robust approach. Conventional wisdom may be acceptable in clinical practice to assess a fractures risk; it becomes questionable when it comes to definitive decisions in oncology [33].

*2.2. SPECT and SPECT CT.* Noteworthy, guidelines do not provide technical recommendations for BS. In many centres BS is limited to anterior and posterior planar images. Standard planar BS can be improved by single-photon emission computerized tomography (SPECT) on selected areas such as the lower thoracic and lumbar spine region or even on the entire axial skeleton (Whole-body SPECT) [33–35]. In cancer patients in general and in PCa in particular, SPECT

enhances both sensitivity and specificity for the detection of BM [34–36]. Even-Sapir et al. have compared BM detection by BS, SPECT, $^{18}$F-Fluoride PET, and $^{18}$F-Fluoride PET/CT in 44 patients with high-risk PCa, including 23 (52%) with BM [36]. The sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) of planar BS were 70%, 57%, 64%, and 55%, respectively, and of SPECT were 92%, 82%, 86%, and 90%, respectively. SPECT identified 62% of the lesions overlooked by planar BS. The major advantage of SPECT is that the added benefit of tomographic imaging required few extra radiation dose and only slight added cost, since most modern cameras now offer the possibility of whole-body SPECT [33]. Nozaki et al. have assessed the value of SPECT in the detection of PCa BM in the lumbar vertebrae in 39 patients, all of them having increased $^{99m}$Tc uptake on BS [37]. Definitive diagnosis of BM was established by MRI. Sensitivity, specificity, PPV, and NPV of bone SPECT were 95.9%, 73.1%, 72.3%, and 96.1%, respectively. Helyar et al. have investigated the additional value of SPECT/CT over Tc-99m BS and SPECT on 50 lesions detected by BS in 40 patients [38]. On reporting the planar study and SPECT scans, reviewers rated 61% of lesions as equivocal. On reporting the SPECT/CT scans, only 8% of lesions were rated as equivocal, 24% were rated as malignant, and 68% as benign.

As a conclusion, SPECT and SPECT/CT provide better accuracy than Tc99m BS in differential diagnosis of lumbar BM. Because whole-body SPECT is time-consuming and not widely available, it is not yet recognized as the "optimal state-of-the art" screening technique, although it is available on most standard BS machine and can be performed at minimal cost increased.

*2.3. Metabolic Imaging, PET, and PET/CT.* Tumour detection, using positron emission tomography (PET) and PET/CT, has emerged as a standard imaging techniques in oncology, since PET/CT has demonstrated higher sensitivity for the early detection of metastases, including BM, in various malignancies [39–41]. Unfortunately, the most widely used metabolic marker, $^{18}$F-FDG PET, has little or even no interest in PCa patients. Ghanem et al. have demonstrated that $^{18}$F-FDG-PET alone or using PET-CT image fusion, is less sensitive than MRI in the detection of bone metastases [42]. $^{18}$F-(Sodium) Fluoride is a high affinity bone-seeking agent usually considered as a promising substitute for $^{99m}$Tc-MDP. In the aforementioned series of 44 high-risk PCa, Even-Sapir et al. has reported sensitivity, specificity, PPV, and NPV of, respectively, 100%, 62%, 74%, and 100% for $^{18}$F-Fluoride PET and of 100% for all parameters for $^{18}$F-Fluoride PET/CT [36]. Of the 156 bone lesions detected by $^{18}$F-Fluoride, 81 lesions (52%), including 34 metastases, were overlooked with normal appearance on planar BS. In contrast, the other aforementioned trial by Ghanem et al. failed to show superiority of $^{18}$F-Fluoride PET over MRI in BM detection [42].

Future studies will focus on newer markers such as $^{11}$C- or $^{18}$F-labeled choline and acetate, $^{11}$C-methionine, and $^{18}$F-fluorodihydrotestosterone [26, 36, 40–44]. Kotzerke et al. have compared $^{11}$C-acetate and $^{11}$C-choline uptake in 12 PCa patients and concluded that the ability of both radiotracers to detect known BM was identical, although interindividual variation was high [45]. Yu et al. have tested the feasibility of $^{11}$C-acetate and $^{18}$F-FDG for the detection and measurement of response to therapy in 8 patients detected with ≥3 BM diagnosed by $^{99m}$Tc BS. $^{11}$C-acetate PET detected BM in all 8 patients, whereas $^{18}$F-FDG PET detected lesions in 6 of the 7 imaged patients [46]. Beheshti et al. have prospectively compared the potential value of $^{18}$F-fluorocholine and $^{18}$F-fluoride PET/CT for BM detection in 38 PCa patients [47]. In case of discrepant results, follow-up was used as validator. Overall, 321 lesions were evaluated in this study. Sixteen malignant osteoblastic lesions were negative with both $^{18}$F-fluorocholine and $^{18}$F-fluoride PET/CT. The sensitivity, specificity, and accuracy of PET/CT for PCa BM detection was 81%, 93%, and 86% for $^{18}$F-fluoride and 74% ($P = 0.12$), 99% ($P = 0.01$), and 85% for $^{18}$F-fluorocholine PET/CT, respectively. In a later study on 70 patients, Beheshti et al. have calculated that the sensitivity, specificity, and accuracy of $^{18}$F-fluorcholine PET/CT in detecting PCa BM was 79%, 97%, and 84%, respectively [48]. Eschmann et al. have published a small study on 42 patients aiming to compare the diagnostic accuracy of $^{11}$C-Choline PET/CT and whole-body WB-MRI [49]. After validation by histology, follow-up, or consensus reading, 88/103 detected lesions were considered as malignant including 44 BMs. Sensitivity, specificity, and accuracy for $^{11}$C-choline PET/CT were 96.6%, 76.5%, and 93.3%, respectively, and for WB-MRI 78.4%, 94.1%, and 81.0%, respectively. Interestingly, however; whole-body MRI was performed without diffusion reading, thus, lowering its performance.

## 3. CT Scanner

CT scanner imaging is central in the diagnosis of musculoskeletal disorders. In bone malignancies, it is not used as a screening test but as a second-line imaging technique to clear-up abnormal BS uptakes remaining unexplained after standard X-ray or to image suspicion of neurological disorders.

Recently, the development of multidetector spiral technology has reawakened the potential interest of CT for early detection of BMs. In a recent analysis, Groves et al. have investigated the value of this technique in BM assessment [50]. They have compared BS and bone imaging from the cranium vertex to the knee by 16-slices CT in 43 patients with known malignancy. BS detected BM in 14/43 and CT in 13/43 patients. There were, however, several discordances. Based on their preliminary analysis, Groves et al. concluded that CT with its present performance is unlikely to replace BS for BM screening. In addition, the total accumulated radiation dose required by whole spine CT precludes the systematic use of this technique for the determination of therapeutic response in clinical trials.

## 4. Magnetic Resonance Imaging (MRI) of the Skeleton

MRI is highly sensitive for detecting BM in cancer patients [25, 31, 51–53]. Its superiority over BS has been repeatedly demonstrated [54–56]. It has been used as a "*gold standard*" to evaluate PET for detecting BM and more recently to

quantify PCa metastases and measure tumour response to therapy [30, 57]. However, the use of MRI in first line is often presented as "not feasible" putting forward its limited availability, costs, or limitations of published series validating the method [30].

MRI characteristics of malignant involvement of the bone marrow are well documented [25, 36, 57–59]. The different MRI patterns of bone marrow involvement in neoplastic disease have been precisely described, so that discriminating metastatic lesions from benign marrow abnormalities such as marrow hyperplasia induced by chemotherapy can easily be made by trained radiologists. MRI appearance of the spinal and pelvi-femoral can be categorized into simple well-defined categories [58, 60]: normal appearance, focal metastatic lesions (focal marrow replacement pattern), which are nodular areas that can be measured, and diffuse marrow infiltration (Figure 1).

The superiority of MRI lies in its ability to detect early tumour cells seeding into the hematopoietic compartment, leading to replacement of the normal hematopoietic marrow and of its fat cells. This technique, thus, identifies BM at an early stage, before host reaction of the osteoblasts becomes visible on BS and X-ray, therefore, increasing sensitivity [25, 28]. Already in 1993, Turner et al. reported on using MRI in 18 PCa patients to resolve conflicting evidence of BM found on bone scans and X-ray [61]. MRI ruled out metastatic disease in 2 of the 8 positive BS and revealed BM in 5 negative BS. All 5 equivocal BS demonstrated no osseous lesions on MRI. In addition, in 6 patients with evidence of BM serial MRI scans following ADT demonstrated radiographic and clinical improvement. In 2000, Walker et al. evaluated whole-body STIR-MRI to detect metastases to liver, brain, and bone as a single examination in women with breast cancer [62]. BM were identified in 11/17 patients, with correlation between findings at whole-body MRI and scintigraphy in 15/17 patients. Daldrup-Link et al. have compared the diagnostic accuracy of whole-body MRI, Tc-99m BS, and FDG-PET for the detection of bone metastases in 39 children aged 2 to 19 years old with various malignancies [28]. Sensitivities for the detection of bone metastases were 90% for FDG-PET, 82% for MRI, and 71% for skeletal scintigraphy. But FDG-PET also produced most false-positive lesions. More recently, our group has evaluated the diagnostic performance and impact on therapy of one-step MRI of the axial skeleton (MRIas) for detecting BM in 66 patients with high-risk PCa [63]. MRIas has been compared to a routine workup based on BS completed with targeted X-ray in cases of equivocal BS findings and with MRI "on request" (MRIor) in case of inconclusive BS/X-ray findings. Sensitivities were 46% for Tc-99m BS alone, 63% for BS/X-ray, 83% for BS/X-rays/MRI, and 100% for MRIas. Corresponding specificities were 32%, 64%, 100%, and 88%. MRIas was significantly more sensitive than any other approach ($P < 0.05$, McNemar). MRIas correctly identified metastases in 7/23 (30%) patients considered negative, and 8/17 (47%) considered equivocal by other strategies, which resulted in altering the initially planned therapy. This increased sensitivity has clearly an added value in routine practice, both in newly diagnosed PCa, to avoid unnecessary radical therapy, and later on in the disease to enable early initiation of treatment with the hope to prevent or delay the complications of metastases.

Are these results sufficient to definitively state that MRI will replace BS as initial and sole imaging modality for staging all PCa patients? The answer is no. The access to MRI technology still needs to be improved and the available MRI machine to be increased. Indeed, it is not often acceptable to delay treatment in high-risk patients waiting to rule out BM. In addition, many authors still advocate the use of BS on the assumption that MRI would be too costy [25, 26, 39]. These data, however, demonstrate that MRI surpasses the current imaging strategy used for bone staging in a high-risk patient population. There is place for large multicentric studies in well-defined groups of patients to assess and confirm the clinical efficacy of MRI as the initial tool for bone staging in PCa.

Further development will focus on whole-body MRI (WBMRI). Hardware and software advances have enabled the acquisition of WBMRI, including conventional sequence (T1, STIR) images covering the entire skeleton, and more recently diffusion-weighted images (DWIs), which facilitates the detection of BM, especially in skeletal areas that are difficult to evaluate on conventional sequences, such as ribs [64–68]. In addition, this allows envisioning an all-in-one metastatic workup (visceral and osseous). Eschmann et al. have compared the diagnostic accuracy of $^{11}$C-Choline PET/CT to whole-body MRI for the staging workup of PCa in 42 patients [44]. Sensitivity, specificity, and accuracy for $^{11}$C-Choline PET/CT were 96.6%, 76.5%, and 93.3%, respectively, and for MRI 78.4%, 94.1%, and 81.0%. Interestingly, 3 BMs had initially been missed by $^{11}$C-Choline PET/CT and were found retrospectively. The author concluded that strength of MRI is excellent image quality providing detailed anatomical information whereas the advantage of Choline PET/CT is high image contrast of pathological foci (Figure 2).

## 5. Conclusion

Correct diagnosis of BM has emerged as major challenge for those who are developing new therapeutic strategies, including those who advocate aggressive local treatment of high-risk localized and locally advanced disease. Tc-99m BS may not be over, but the time when patients would be treated on suspicion rather than on robust evidences is passed. Many technologies including metabolic imaging by PET and MRI are indeed rapidly gaining interest in the everyday management of PCa patients. As it is for modern treatments, the diagnosis strategies will be multidisciplinary by nature and involve crossfertilization between nuclearists, urologists, and radiation oncologists.

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*Research Article*

# Radical Prostatectomy: An Option for High-Risk Prostate Cancer

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*Introduction*. High-risk prostate cancer represents a therapeutic challenge. The role of radical prostatectomy (RP) in patients with extreme PSA values is under discussion. *Material and Methods*. We retrospectively analysed our data of 56 consecutive patients with preoperative PSA ≥ 40 mg/mL undergoing open radical retropubic prostatectomy from 1999 to 2009. Patient survival and time to PSA recurrence were recorded, and the Kaplan-Meier survival analysis was performed. Postoperative quality of life and functional status were investigated using a SF-12 questionnaire and determining the number of pads used per day. *Results*. Overall 56 patients were available for followup after a median time of 83.84 months. Locally advanced carcinoma was present in 84% while 16% of patients had organ-confined stages. A positive nodal status was observed in 46%. Overall survival was 95% at five and 81% at 10 years. Cancer-specific survival was 100% for five years and 83% for 10 years. Corresponding biochemical recurrence-free survival was low (52% and 11%, resp.). Quality of life and functional outcomes were favourable. *Conclusions*. In patients with PSA ≥ 40 mg/mL, RP allows long-term control, exact planning of adjuvant treatment, and identification of curable disease.

## 1. Introduction

Prostate cancer is an important medical issue with a high complexity regarding stage classification and risk-adapted multidisciplinary treatment. As the consensus towards the therapy of localised prostate cancer is broad, radical prostatectomy (RP) is an established surgical approach based on reliable clinical data. High-risk prostate cancer is defined as PSA > 20 ng/mL, Gleason 8–10 or clinical stage ≥ T2c. RP is also considered as first-line treatment for higher-risk strata whereas the scientific evidence for patient outcomes, especially those with elevated PSA values greater than 50 ng/mL, is comparably low [1]. Based on our own single centre experience and the implementation of available published data, our investigation targets this relevant clinical topic.

## 2. Material and Methods

We retrospectively analysed our data of 56 consecutive patients with an elevated PSA ≥ 40 ng/mL who underwent radical retropubic prostatectomy with iliac lymphadenectomy from 1999 to 2009 with followup to October 2010. The template of LAD consisted in external, internal iliac, and obturatorial lymph nodes. A nerve-sparing procedure was not conducted. We examined patient survival, time to PSA recurrence, and cancer-related survival. Complete followup was available for 54/56 patients (96%). A Kaplan-Meier analysis was performed to analyse overall (OS) and cancer-specific survival (CSS) and time to biochemical recurrence (BCR), which was defined as postoperative PSA ≥ 0.4 ng/mL or PSA rise while receiving androgen deferral treatment. To assess postoperative quality of life, a SF-12 questionnaire was used. For the evaluation of postoperative continence, the number of used pads per day was interrogated using a patient questionnaire.

## 3. Results

In our cohort, 56 consecutive patients with a preoperative PSA ≥ 40 ng/mL (median: 54.2 ng/mL) were available for the analysis. Mean age at surgery was 66.81 years. Median followup was 83.3 months (IQR: 37.57 to 109.43). Patient characteristics, the distribution of preoperative staging, biopsy Gleason's score, and clinical stages are demonstrated in Table 1.

With regard to pathological staging, a predominance of locally advanced cancer is characterized by 84% stage pT3/pT4 prostate carcinoma whereas, in 16% of patients,

Table 1: Preoperative patient characteristics (IQR: interquartile range).

| $n$ = | 56 |
|---|---|
| Age, mean (IQR) | 66.81 y (61.2–70.1) |
| PSA, median (IQR) | 54.2 ng/mL (46–79.1) |
| Followup, median (IQR) | 84.83 months (37.57–109.43) |
| Gleason's score (biopsy) | |
| ≤6 | 25 (44%) |
| 7 | 20 (36%) |
| 8–10 | 11 (20%) |
| Clinical stage | |
| cT1 | 10 (18%) |
| cT2 | 9 (16%) |
| cT3/4 | 37 (66%) |

Table 2: Postoperative patient characteristics.

| | |
|---|---|
| Pathologic Gleason's score | |
| ≤6 | 17 (30%) |
| 7 | 26 (46%) |
| 8–10 | 13 (24%) |
| Pathologic stage | |
| pT2 | 9 (16%) |
| pT3 | 20 (36%) |
| pT4 | 27 (48%) |
| Pathologic nodal status | |
| N0 | 29 (54%) |
| N+ | 25 (46%) |
| Surgical margin status | |
| Negative | 30 (54%) |
| Positive | 26 (46%) |
| Hormonal therapy | |
| Adjuvant | 21 (38%) |
| Neoadjuvant | 17 (30%) |
| None | 18 (33%) |
| Adjuvant RT | |
| Yes | 28 (50%) |
| No | 28 (50%) |
| Quality-of-life assessment (SF-12): general state of health | |
| Excellent | 6% |
| Very good | 25% |
| Good | 50% |
| Fair | 6% |
| Poor | 13% |
| Continence assessment (pad usage) | |
| 0-1 | 58% |
| 1 | 29% |
| 2 or more | 13% |

the prostate carcinoma was organ confined. A positive nodal status was observed in 46% of patients in our study collective.

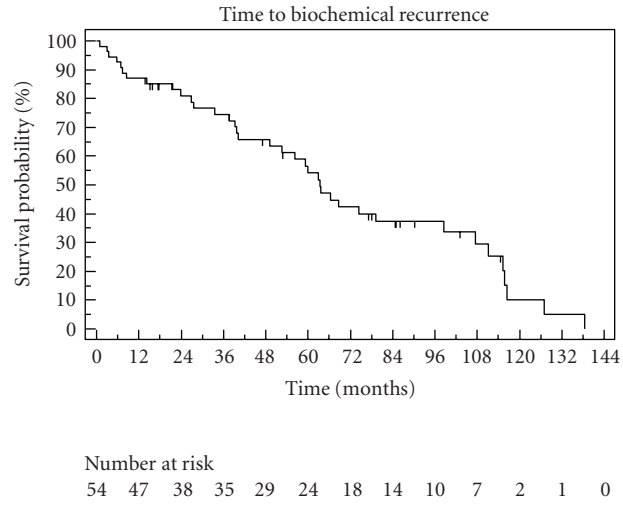


Figure 1: Biochemical recurrence.

Pathologic Gleason's scores of ≤6 were observed in 30% of cases, the incidence of Gleason's scores ≥8 was 24%. Surgical margins were positive in 26 patients (46%). The majority of patients (68%) underwent additional hormonal treatment, which was applied according to institutional protocols. From 1999 to 2004, 17 patients (30%) received neoadjuvant hormone ablation with LH-RH analoga. Adjuvant hormonal therapy was applied to 38% either by orchidectomy or postoperative pharmacological (LH-RH agonist) androgen withdrawal. Half of the patients received adjuvant radiation therapy. Postoperative pathological staging, grading, and adjuvant treatment measures are summarized in Table 2.

The Kaplan-Meier curves describing overall survival, CSS, and biochemical recurrence are shown in Figures 1, 2, and 3. Overall survivals at five and ten years were 95% and 81%. The biochemical recurrence-free survival was 52% at five and 11% at ten years. Cancer-specific survival varied only marginally from OS (100% in five years, 83% in ten years), as only two of four deaths in our cohort were caused by prostate cancer. Postoperative continence and quality-of-life results were available through 70% of returned questionnaires in our study. Regarding postoperative quality of life, 75% of the patients described their general state of health as good or very good (SF-12). At last followup, 88% in our study at used maximum one pad per day (Table 2).

## 4. Discussion

In the PSA era, the proportion of men treated with RP for high-risk prostate cancer has decreased while in contrast the number of patients undergoing surgery for low-risk cancer is increasing. Nevertheless, the currently used risk groups remain predictive of patient outcomes [1]. The pretreatment risk stratification for patients diagnosed with high-risk prostate cancer is commonly based on the classification system of D'Amico et al. which includes PSA value (>20 ng/mL), biopsy Gleason's score (8–10), and clinical T-stage (cT2c or more) [2]. Based on the same data, for radical prostatectomy risk, stratification is available not only

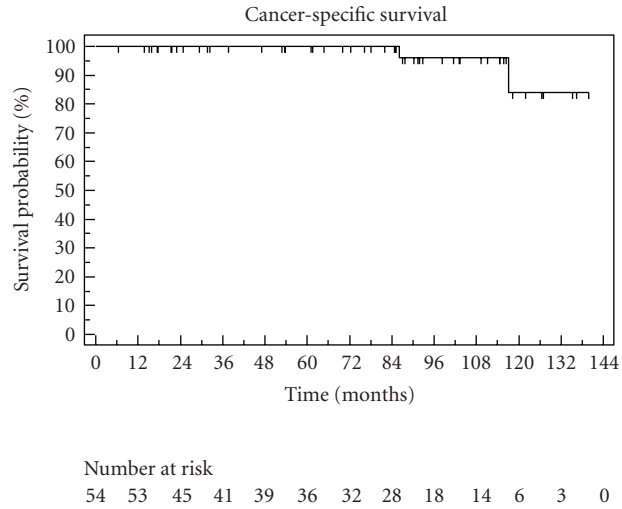


Figure 2: Cancer-specific survival.

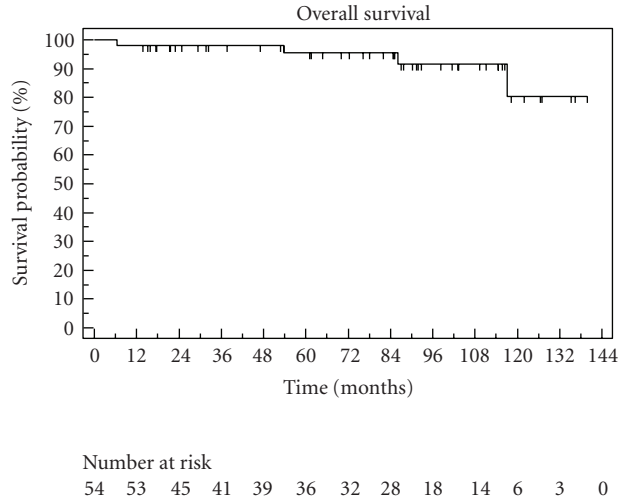


Figure 3: Overall survival.

for biochemical recurrence but also for disease progression and survival [3]. This observation is crucial as the impact of biochemical recurrence does not automatically influence clinical progression and overall survival. To improve prostate cancer risk assessment, Cooperberg et al. established a scoring system based on the CaPSURE database which allows the prediction of clinically more relevant endpoints such as development of metastases, cancer-specific mortality, and overall survival [4]. In our cohort, we reviewed patients with a PSA threshold of >40 ng/mL in order to assess the outcome of individuals with an elevated risk profile.

In a retrospective, multi-institutional analysis of 712 patients, Spahn et al. assessed additional high-risk factors for individuals with pretreatment PSA > 20 ng/mL undergoing RP. Biopsy Gleason's score ≥8 was identified as a strong predictor of progression and survival leading to a cancer-specific mortality of 35% in 10 years, whereas biopsy Gleason's scores smaller or equal to 7 lead to a low cancer-specific mortality of 5% [5]. In their review, Karnes et al. specify the outcome of 1513 men from the Mayo Clinic cohort that were classified into the high-risk group according to the D'Amico criteria. Median followup was 7.7 years, and survival analysis revealed a ten year overall survival of 80% (95% cancer specific). Also, 55% of patients were free of biochemical recurrence in ten years, 90% showed no local recurrence, and 89% no systemic progression [1].

In our study, we observed comparable long-term results of 95% overall survival at five years and 81% at 10 years. Only two patients (4%) died from prostate cancer. The biochemical recurrence-free rate at five years was 52%, however, only 11% at 10 years. Apart from the advantage of local disease control, 16% of our patients showed an organ-confined potentially curable tumour stage. Inman et al. analysed the Mayo Clinic data with PSA values between 50 and 100 ng/mL after radical prostatectomy and observed a lower biochemical relapse rate of 40% at 10 years [6]. Another study group observed PSA failures of 27% at five years for patients with elevated PSA of 50 to 100 ng/mL [7]. In a retrospective analysis, Gontero et al. found 48 patients with a PSA ≥ 100 ng/mL treated with RP. In this subset of patients, 8.3% could be cured by surgery alone at a median followup of 78.8 months. Ten-year cancer-specific survival accounted for 79.9%, however, significantly decreased in comparison to lower PSA thresholds in their study [8]. Meng et al. observed that, in the USA, patients with high-risk prostate cancer are significantly less likely to be treated by RP than by primary hormonal or radiation therapy [9]. Nevertheless, the aforementioned cancer-specific and overall survival rates indicate that high-risk prostate cancer patients stand to benefit from radical prostatectomy. The variety of biochemical outcomes in the literature may be the result of different application of adjuvant and salvage therapies in the respective cohorts. In our study, adjuvant and neoadjuvant treatment was applied to 38% and 30% of patients. Fifty percent underwent adjuvant radiation therapy. Walz et al. investigated the pathological characteristics and rates of biochemical recurrences after RP in men with advanced prostate cancer according to the D'Amico classification. The authors observed favourable pathology (organ-confined, negative surgical margins, Gleason's score ≤7) in 13.7% of clinical T3 carcinoma, 16.4% of patients with a biopsy Gleason's score ≥8, and 21.4% for the D'Amico high-risk group. Patients with an elevated PSA ≥ 20 mg/mL showed a favourable pathology in 21.6% of cases. The presence of more than one risk factor led to a decrease in biochemical recurrence-free survival [10]. In the authors's opinion, it is questionable, whether a PSA of >20 or >40 is able to discern a high-risk PCA group with regard to operative treatment and outcome although biochemical relapse rates occur to grow with high preoperative levels of PSA.

From our own observation and in line with the Mayo Clinic's analysis with about 60% of high-risk stratified patients presenting with organ-confined stages, allowing long-term local disease control in 90% of all patients, there is no rationale to deprive patients of radical surgery [1]. The fact that primary RP goes in line with fundamental pathologic information offers the possibility to apply adjuvant treatment to selected patients and to avoid hormonal or

radiation overtreatment. Immediate androgen deprivation after radical treatment has shown to improve patient survival in locally advanced stages [11], and adjuvant androgen withdrawal has proven to be beneficial for patients with positive nodal status [12] while adjuvant radiotherapy can preserve local control in extraprostatic growth and positive surgical margins [13]. In a Cochrane database review, Kumar et al. found no significant improvement on overall survival by neoadjuvant hormonal treatment prior to RP [14]. As the patient cohort in our investigation is recruited from 1999 to 2009, in an early subset of patients (17) from 1999 to 2004, neoadjuvant hormonal treatment has been performed.

Important issues regarding the surgical treatment of high-risk prostate cancer are operative feasibility, quality of life, and functional outcome. In a single centre, single surgeon study of 288 men treated with radical prostatectomy in a high-risk setting (defined as PSA ≥ 15 ng/mL, ≥cT2b or Gleason's score 8 to 10), Loeb et al. observed a potency rate of 62% and a continence rate of 92% within 10 years [15]. Gontero et al. compared a series of patients with clinically advanced prostate cancer undergoing RP to a control group of clinically organ-confined disease and found no significant differences in surgical morbidity apart from transfusion rate, operation time, and lymphoceles [16]. In our investigation, 75% of patients describe themselves in a good or very good status of health (SF-12) at followup. Favourable functional outcome is documented by a rate of 88% of patients requiring at maximum one pad per day. Nevertheless, our analysis is limited by its retrospective design, the fact that it is based on single center data and the variety of applied (neo)adjuvant treatment measures. Regarding postoperative Gleason's scores, it has to be considered that the number of low Gleason's grades is presumably confounded by tumour regression due to the preoperatively applied antihormonal treatment.

## 5. Conclusions

Although RP might be inadequate as solitary therapeutic approach for high-risk prostate cancer in a subset of patients, the procedure allows surgical control with good quality of life and satisfying functional outcome. Accurate pathologic information and improved patient selection for individual adjuvant treatment is possible. Even in individuals presenting with elevated PSA ≥ 40 ng/mL, RP offers not only long-term disease control in general but also a curative approach in at least 16% of patients with organ-confined disease.

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*Review Article*

# Sense and Nonsense of an Extended Pelvic Lymph Node Dissection in Prostate Cancer

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Lymph node metastases associated with prostate cancer (PCa) has been shown to be a poor prognostic factor. The role of pelvic lymph node dissection (PLND) itself in relation to survival remains unclear, however. A Medline search was conducted to address this issue. The following conclusions were drawn. Only recently, improved survival due to completion of radical prostatectomy (RP) (compared to abandoning RP) in known or presumed lymph-node-positive patients has been shown. Lymph node sampling can only be considered representative if an adequate number of nodes is removed. While several authors have suggested that a therapeutic benefit in patients undergoing RP is not provided by PLND, the reliability of these studies is uncertain. Contrary to this, several studies have indicated the possibility of long-term survival even in the presence of limited lymph node metastases. The role and timing of initiation of adjuvant androgen deprivation therapy (ADT) in patients who have node-positive disease after RP is controversial. Recent studies suggest that delaying ADT may not adversely impact survival.

## 1. Introduction

Lymph node metastases in men diagnosed with PCa has been shown to be a poor prognostic factor for biochemical recurrence (BCR) and survival [1–3]. As part of the stage migration in PCa during the PSA era, the incidence of positive lymph nodes has decreased steadily [1, 4]. Nevertheless, accurate identification and staging of men with lymph node metastases allows more precise prognostication and may have important implications on the initiation of adjuvant therapy [5]. Surgical excision and histological examination of the pelvic lymph nodes provides the most accurate staging information regarding pelvic lymph node status [6–8]. The role of PLND in relation to survival remains, however, unclear. Furthermore, switching from a limited nodal dissection to an extended one (ePNLD) is associated with a 14.6% complications rate which in most papers is higher than that of a more limited dissection [8]. Of course, the benefit of performing an ePLND must outweigh the elevated risk of complications.

We sought to review the available literature concerning the role of PLND and RP on survival outcome.

## 2. Evidence Acquisition

A Medline search was conducted to identify original articles addressing the role of PLND in PCa. Keywords included prostate cancer, pelvic lymph node dissection, and radical prostatectomy. All of the keywords are within the Medical Subject Headings (MeSH) database. Original articles with the highest level of evidence were identified and were critically reviewed.

## 3. Evidence Synthesis

*3.1. Localization of Nodes Draining the Prostate.* The lymphatic drainage of the prostate gland has been described more than 100 years ago [9]. Three regions are concerned: common iliac, external iliac, and hypogastric. These anatomic findings have been confirmed clinically through extended nodal dissections revealing positive nodes outside the obturator fossa, namely, around the common iliac artery and the hypogastric pedicle in 22% and 29%, respectively [10]. Therefore, all these sites have to be considered while performing an extended pelvic lymph node dissection.

*3.2. Number of Nodes Removed.* Since the number of positive lymph nodes detected is strongly correlated to the number of nodes removed, lymph node sampling can only be considered representative if an adequate number of nodes and all relevantly located nodes are removed [4–8, 11–16]. An autopsy study by Weingärtner et al. suggests that 20 lymph nodes must be removed for an adequate PLND [17]. Several studies have shown this requirement to be technically feasible by harvesting a comparable number of lymph nodes in vivo [2, 7, 8, 13, 18, 19]. Reports on patients who underwent more limited PLND might be misleading and incomplete lymph node sampling probably will not provide an accurate prognostic factor for survival. A certain percentage of cases would be considered lymph node negative (pN0) because metastases were not detected merely by the limited extent of PLND performed. Such patients would be left with residual tumor and perhaps deprived of the chance of cure.

However, maybe being even more important than the absolute number of nodes, the anatomical boundaries of PLND should be considered since there is a natural variability in the number of nodes encountered in one patient compared to another. Moreover, as is the case in radical cystectomy, the differences in methods by which lymphatic tissues are collected, transported, and processed by the pathologist could lead to a significant difference in nodal count. Thus, the absolute number of nodes counted might be misleading [20].

Irrespective of the nodal status, an increased absolute number of nodes removed have been suggested to be associated with better cancer control for some tumors, such as colon or bladder cancer [21]. In PCa, this has been tested in only one retrospective cohort, without any benefit for relapse [14]. But major limitations must be highlighted, such as the median number of removed nodes (only 9), and a statistical analysis performed on only 174 patients with positive nodes. Using the SEER database, a positive relationship was observed between the total number of nodes removed, and PCa-specific survival. Surprisingly, the difference was observed in PLND with >4 nodes, which is far below the expected number of an ePLND [13, 16]. Confirmatory analysis based on prospective data is mandatory.

*3.3. Indications for PLND.* Indications for PLND are subject to debate. The guidelines of the European Association of Urology indicate that a PLND should be undertaken in men with intermediate (cT2a, PSA 10–20 ng/mL, biopsy Gleason score 7) or high-risk (>cT2b, PSA >20 ng/mL, Gleason score ≥8) PCa, when the nomogram-estimated risk for positive nodes exceeds 7% [22]. Meanwhile, there are other authors who recommend performing ePLND in all patients with a PSA level of ≥10 ng/mL, and in all patients with a PSA level of <10 ng/mL with a Gleason score >6 [4]. The definition of the indication for PLND lies not within the scope of this paper, nor is the incorporation of sentinel node sampling within the diagnostic armamentarium.

*3.4. pN0 Patients.* Several authors have suggested that a therapeutic benefit in patients undergoing RP is not provided by PLND. DiMarco et al. reported that the extent of lymphadenectomy does not affect cancer outcome in lymph node negative cases thereby making the impact of PLND negligible in the overall population, or in patients stratified as having high-risk PCa based on the D'Amico classification (1059 high risk patients) [23]. This single institution analysis on a cohort of 7036 patients undergoing RP with or without PLND over a 13 yr time span has several limitations. Since conclusions were drawn from a pN0 PCa population of which 71% of patients had Gleason score ≤6, 95% had organ confined disease and only 26% had a PSA >10 ng/mL, no definite conclusions can be drawn for the entire PCa population, especially for patients with high risk PCa or lymph node invasion (pN1). Moreover, the mean number of nodes removed per patient in this study was only 9. Bearing in mind the strong correlation between the total number of nodes removed and the number of positive nodes detected, underestimation of lymph node invasion is inherent to more limited PLND rendering any conclusion on survival based on a less than extended PLND doubtful. Finally, therapeutic outcome in terms of BCR was the same between the patients operated at the beginning of the author's experience with a more extensive PLND compared to those operated 10 yr later with a minimal PLND despite a significant shift in tumor stage. It cannot be excluded that more extensive PLND in their early experience might have had an influence on recurrence and survival because one would expect a poorer outcome for the earlier group, considering the higher frequency of locally advanced PCA in this era.

Murphy et al. showed in a similar population of 964 pN0 patients with low median PSA of 6.2 ng/mL, of which only 36.5% of patients had Gleason score ≥7 and 99.5% had clinically organ confined disease, that the number of nodes removed was not significantly associated with BCR [24], thereby questioning the role of PLND. Again this type of population does not warrant conclusions for PCa patients at higher risk of disseminated disease. Moreover, the anatomical extent of the PLND performed was not captured in this study. The internal iliac region is often omitted when performing PNLD, although lymph node metastasis is said to be found in this region in 62% of cases [13]. The absence of knowledge on the regional extent of PLND might introduce an inherent bias.

Bhatta-Dhar et al. also failed to find a statistically significant difference in the 6-year BCR-free survival rate in a low-risk PCa population who did or did not undergo PLND [25]. Conclusions for the entire population of PCa patients

(with intermediate and high-risk patients included) cannot be drawn, especially not for those with pN1 PCa. Moreover, a followup of 6 years is too short when considering the typical protracted natural history of PCa.

In summary, the reliability of studies showing that PLND does not confer a survival benefit in pN0 is uncertain.

A last comment regards the definition of pN0 patients. Are the analyzed nodes really negative? In a retrospective single centre analysis of 4,611 patients, Masterson et al. showed a positive impact on BCR-free survival resulting from an increased total number of nodes removed in pN0 patients [14]. It was speculated that this might have been due to cellular disease that had escaped identification, but was treated effectively with ePLND. This may indeed be considered since using modified pathological analysis such as systematic immunohistochemistry analysis [26] or RT-PCR [27] increases the node positivity by 13.3% and 26.6%, respectively. Interestingly, patients with an upstaged nodal status using those techniques showed the same cancer-related outcomes compared to those who were initially staged pN1.

*3.5. pN1 Patients.* Although no prospective randomized clinical trials are available, several studies have indicated the possibility of long-term survival even in the presence of limited lymph node metastases [3, 5, 6, 16, 18].

Based on a population of 367 patients who underwent RP and extended PLND, Bader et al. concluded that some patients with minimal metastatic disease in the lymph nodes remain free of BCR for more than 10 years after surgery without adjuvant treatment [18]. This finding implies a possible therapeutic effect of PLND, especially since in this report any adjuvant treatment was deferred until symptoms of disease progression occurred.

Likewise, Allaf et al. showed that a significant benefit in BCR-free survival may exist for certain subgroups of pN1 PCa patients undergoing RP with extended PLND [5]. In this single centre study including 4,000 patients, the outcomes of RP with limited PLND (all performed by surgeon A) were compared to those of RP with extended PLND (performed by surgeon B). There was a trend towards improved BCR-free survival in patients who underwent extended dissection. In a subset of patients with nodal involvement and less than 15% positive lymph nodes, there was a statistically significant difference between PLND techniques with respect to BCR. However, given the low number of patients with positive lymph nodes, this study could be underpowered.

The same group retrospectively analyzed a population of 3,264 patients undergoing RP with extended PLND [28]. Nodal involvement was present in 143 patients (4.4%), and these patients only underwent adjuvant treatment after clinical disease recurrence occurred. In the multivariate analysis, 15% or greater positive lymph nodes was a significant predictor of BCR. Stratifying patients simultaneously according to the 3 strongest prognostic factors made it possible to define a subset of pN1 patients that showed 5-year BCR-free survival of 52% (i.e., for patients with <15% positive lymph nodes and Gleason score ≤7 and absence of seminal vesicle invasion). An important limitation of this study was that BCR was defined as end-point, rather than clinical progression or survival.

The concept and prognostic significance of the percentage of positive lymph nodes or lymph node density was further elaborated in a single centre retrospective analysis of 235 pN1 patients after RP with extended PLND [2]. 69% of these patients did not undergo any adjuvant treatment. Lymph node density was defined as the number of positive nodes divided by the total number of nodes removed. When stratified by lymph node density, patients with a density of 20% or greater were at higher risk for clinical recurrence compared to those with a density of less than 20% (RR: 2.31; $P < 0.001$). In patients with lymph node density less than 20% the mean 10-year clinical recurrence-free survival rate was 72% compared to 47% in those with a lymph node density 20% or greater.

Probability of long-term survival after RP with or without subsequent androgen deprivation therapy, even with the presence of limited lymph node metastases, was also observed in a study of 13,020 patients undergoing RP obtained from the Surveillance, Epidemiology, and End Result Program (SEER) [16]. Patients undergoing excision of at least 4 lymph nodes (node-positive and node-negative patients) or more than 10 nodes (only node-negative patients) had a lower risk of prostate cancer-specific death at 10 years than did those who did not undergo PLND. This is only possible if a percentage of patients with macroscopic as well as microscopic lymph node invasion is cured by more extensive PLND. Using the SEER database poses several evident limitations: lack of information regarding adjuvant hormonal treatment, lack of information on other patient characteristics, inability to control for margin status, and lack of PSA data for some of the patients included.

A large retrospective analysis from the Mayo Clinic confirmed the finding that RP may offer long-term survival to patients with pN1 PCa [11]. In 507 patients identified as pN1 at RP with extended PLND, cancer-specific survival (CSS) depended amongst other variables on the degree of lymph node involvement. Ten-year CSS was as high as 86%. While in this last study 90% of patients received adjuvant ADT, Schumacher et al. reported on 122 pN1 patients after RP who did not receive any ADT. They confirmed good long-term BCR-free survival and CSS for patients with low-volume nodal burden after RP [6]. For patients with 1 positive lymph node, 10-year BCR-free survival and CSS were 24.7% and 72.1%, respectively. In patients with 2 positive lymph nodes, 10-year BCR-free survival and CSS were still 11.8% and 79.1%, respectively.

The exact definition of "low-volume nodal burden" portending good survival was further elaborated by Fleischmann et al. in a single-centre study of 102 node-positive patients who did not receive adjuvant ADT [15]. On multivariate analysis, the diameter of the largest metastasis was the strongest prognostic factor for all end points (BCR, CSS, and overall survival). On the other hand, Briganti et al. emphasize on the absolute number of nodes affected when they state that ≥2 positive nodes represent a significant cutoff value for predicting CSS in patients with node-positive PCa after RP [7, 8]. Important limitations of this study were the fact

that all patients were submitted to adjuvant ADT, differences in population characteristics between the two contributing institutions as well as differences in the way the lymph nodes were sent for pathological examination.

*3.6. cN1 Patients.* Until recently, there was only limited data to support completing RP in known or presumed lymph-node-positive patients. Using a population-based database, Engel and Bastian showed that patients with pN1 disease at frozen section analysis may experience improved survival when RP is completed, compared to patients with abandoned RP [29]. This obvious advantage should encourage urologists to complete RP, regardless of lymph node status, and therefore omit frozen section analysis of lymph nodes. Their conclusions were based on 13,805 patients with histologically confirmed PCa included in the Munich Cancer Registry. Differences in survival were impressive, and in favor of patients with completed RP, even in node-positive cases. Of course, a formal prospective trial would be the only way to get a definitive answer on this issue, but this is unlikely to ever be done.

*3.7. Adjuvant Treatments.* Although ADT has a well-defined role in patients who have metastatic disease and in patients who are undergoing radiotherapy for high-risk disease, its role in patients who have node-positive disease after RP is controversial. Messing et al. reported the results of a randomized, controlled clinical trial in men with pN1 after RP, comparing life-long immediate adjuvant ADT with ADT at the time of metastatic disease. The study reported a significant advantage in progression-free survival and overall survival that favored early adjuvant ADT [30]. Given the potential for long-term adverse effects associated with ADT, such as osteoporosis, cardiovascular disease, diabetes, and mood disorders, delaying the initiation of ADT until documented BCR may spare patients significant treatment-related toxicities. In a large cohort of 731 pN1 patients after RP, Wong et al. compared administration of adjuvant ADT with patients who did not receive adjuvant ADT. The results suggest that the delay of ADT may not adversely impact CSS, nor overall survival [31]. This cohort of patients was constructed using linked SEER—Medicare data implying several limitations as already has been mentioned before. In a similar setting, Schröder et al. reported on the result of EORTC 30846, which examined the role of immediate versus delayed ADT in patients who had node-positive disease and who did not undergo RP. There was no difference in overall survival between the early and deferred ADT arms [32]. The most likely reason for these conflicting results is the difference in indication for initiation of ADT in the groups that were initially observed. In the study by Messing et al., patients were only started on ADT if they developed clinical metastases, which is associated with a high risk of both CSS and overall mortality. However, in more recent trials, post-RP monitoring of PSA became routine and patients in these series likely were followed for BCR. Hypothetically, treatment with ADT at the time of BCR may be successful in the treatment of micrometastatic disease and in the prevention of the onset of metastatic disease (and possibly subsequent death from PCa). This hypothesis may be a possible explanation for the improved outcomes in the delayed treatment arm of the above-mentioned series [31, 32]. Further studies support such hypothesis. D'Amico et al. proved a PSA doubling time of less than 3 months is a surrogate end point of CSS. Therefore, these men are most likely to benefit most from the extended, relatively symptom-free interval provided by early salvage ADT [33]. Whether or not adding ADT at the time of BCR actually improves survival remains to be clarified. In the literature, only few retrospective papers show evidence of some improvement in CSS and even in overall survival [34, 35]. Anyhow, the promising survival rate of patients with very low-volume nodal burden after surgery alone (RP and PLND) makes the value of routine immediate ADT in all patients with lymph node metastases at least questionable, especially when considering the negative side effects [18].

Another interesting aspect of adjuvant therapy was alluded to by da Pozzo et al. [19]. This group was the first to investigate the role of ADT with or without radiation therapy in node-positive patients. All 250 patients underwent RP with extended PLND and were submitted to adjuvant ADT in this single centre report. They found a significant protective role for adjuvant ADT together with radiation therapy in CSS. Important limitations of this study are the two different radiation therapy regimens that were used (26% underwent irradiation of the prostatic bed only, while 74% also underwent pelvis irradiation) and data regarding quality of life related to the delivery of adjuvant radiation therapy were not obtained. Therefore, it can so far only be considered as hypothesis generating and cannot be considered standard of care.

## 4. Conclusions

From this Medline search concerning the role of PLND and RP on survival outcome, the following conclusions were drawn. First, lymph node sampling can only be considered representative if an adequate number of nodes and all relevantly located nodes are removed. Second, while several authors have suggested that a therapeutic benefit in patients undergoing RP is not provided by PLND, the reliability of these studies is uncertain. Third, several studies have indicated the possibility of long-term survival even in the presence of very limited lymph node metastases provided patients had an extended PLND. Fourth, improved survival after completion of RP (compared to abandoning RP) in known or presumed lymph-node-positive patients has recently been shown. Fifth, although ADT has a well-defined role in patients who have metastatic disease or in patients with high-risk localized disease undergoing radiotherapy, its role in patients who have node-positive disease after RP is controversial. Historically, a significant advantage in progression-free survival and overall survival was attributed to immediate adjuvant ADT after RP. However, this evidence was acquired in a pre-PSA, small-sized prospective randomized trial in which most patients had high-volume nodal tumor burden. The translation of those results towards contemporary pN1 patients—who frequently have

low-volume nodal tumor burden in an extended PLND—is problematic.

## Authors' Contribution

Anthony Van Baelen and Nicolas Mottet contributed equally to the paper.

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*Research Article*

# The Long-Term Outcomes after Radical Prostatectomy of Patients with Pathologic Gleason 8–10 Disease

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*Background*. We explored the long-term clinical outcomes including metastases-free survival and prostate cancer-specific survival (PCSS) in patients with pathologic Gleason 8–10 disease after radical prostatectomy (RP). *Methods*. We report on 91 patients with PCSS data with a median followup of 8.2 years after RP performed between 1988 and 1997. Cox regression and Kaplan-Meier analysis were used to evaluate year of surgery, pathologic stage, and surgical margin status as predictors of PCSM. *Results*. Median age was 65 years (IQR: 61–9), and median PSA was 9.7 ng/ml (IQR: 6.1–13.4). Of all patients, 62 (68.9%) had stage T3 disease or higher, and 48 (52.7%) had a positive surgical margin. On multivariate analysis, none of the predictors were statistically significant. Of all patients, the predicted 10-year BCR-free survival, mets-free survival, and PCSS were 59% (CI: 53%–65%), 88% (CI: 84%–92%), and 94% (CI: 91%–97%), respectively. *Conclusions*. We have demonstrated that cancer control is durable even 10 years after RP in those with pathologic Gleason 8–10 disease. Although 40% will succumb to BCR, only 6% of patients died of their disease. These results support the use of RP for patients with high-risk localized prostate cancer.

## 1. Introduction

Since the advent of widespread prostate-specific antigen (PSA) testing in the late 1980s and early 1990s, PC detection has increased with a concomitant downward-shift in stage [1, 2]. In addition to PSA, the introduction of the anatomic radical retropubic prostatectomy (RP) [3, 4], breakthroughs in radiotherapy delivery [5], and systemic chemotherapeutic agents [6] have resulted in a 30% mortality reduction [7]. Despite the stage shift and treatment improvements, 15% of contemporary patients will present with high-risk localized prostate cancer [8]. Contemporary high-risk disease is generally defined by high Gleason score rather than elevated PSA or advance stage due PSA testing and digital rectal examination [8, 9]. Unfortunately, 50% of patients with high-risk disease will succumb to biochemical failure within 10 years [10, 11].

Although there are no randomized trials that support the use of RP for patients with high-risk disease, recent retrospective studies lend credence to the use of RP as an effective therapy for this group of patients [12, 13]. The renewed interest is based on multiple benefits of surgery. First, it provides excellent local control. Second, it better defines the extent of disease than biopsy alone [14]. Third, with prostate removal, PSA failures can be more easily detected. Fourth, radiation can be given in the adjuvant or salvage setting whereas surgery after radiation is associated with high complication rates [15].

In that context, we hypothesized that patients with pathologic Gleason 8–10 disease may have better long-term clinical outcomes after RP than previously thought. Thus we explored the long-term clinical outcomes including metastases-free survival and prostate cancer-specific survival (PCSS) in these high-risk patients after RP.

## 2. Materials and Methods

We retrospectively analyzed charts of patients who underwent radical prostatectomy (RP) between 1988 and 1997 at Virginia Mason Medical Center (VMMC). No patient received neoadjuvant therapy. One of the authors (R. Gibbons) logged clinical and pathological data into a prospective database from 1988 to 1999. After 1999, the records were maintained electronically with institutional review board (IRB) approval. PSA testing began in 1988 at VMMC. All patients were operated between 1988 and 1997. We subselected for a cohort of 91 patients that had pathologic Gleason 8 disease or higher and had postoperative PSA data available. Of all patients, 66 (72.5%) underwent radical retropubic prostatectomy (RRP) and 25 (27.5%) underwent radical perineal prostatectomy (RPP). All specimens were evaluated by VMMC pathologists. Specimens were processed as half mount specimens and serially sectioned at 5 mm intervals. Alternate 5 mm sections were fixed in formalin and were paraffin embedded. From 1988 to 1992 pathological tumor stage was recorded according to the Whitmore-Jewett classification and later converted to the 1992 AJCC staging guidelines [16, 17] From 1992 to 1997 the 1992 AJCC staging system was used for clinical and pathological staging.

From 1992 to 1997 tumors were routinely classified according to the Gleason grading system [18]. Before 1992 tumor grade was recorded as well differentiated (I), moderately differentiated (II), and poorly differentiated (III). To recode these data we followed the paradigm outlined by Roehl et al., in which well-differentiated tumors are classified as Gleason sum 3, moderately differentiated tumors are assigned Gleason sum 6, and poorly differentiated tumors are assigned Gleason sum 9 [19]. Positive surgical margins were recorded as presence of cancer cells against the inked resection margin.

Serum PSA testing was initiated at VMMC in 1988. Since that time patients were followed at least quarterly for 2 years, then at least biannually for 2 years, and then at least annually. Biochemical recurrence was defined as PSA greater than 0.1 ng/mL. Metastases were diagnosed based on technetium-99m-based bone scintigraphic studies, and computed tomography cross-sectional imaging was used in equivocal cases. Adjuvant or salvage hormonal and/or radiotherapy were delivered according to individual surgeon preference. Adjuvant therapy was defined as adjunctive radiotherapy in the absence of PSA recurrence (PSA $<$ 0.1 ng/mL) given within 6 months of surgery. Neoadjuvant hormonal therapy was defined as hormone delivery prior to surgery. Cause of death was ascertained according to detailed chart review or was obtained from the VMMC cancer registry. The cancer registry uses links with the Washington State Death Certificate Office. PC must be the first listed cause of death on the certificate for a patient to be classified as having died of PC.

Prostate cancer-specific mortality was analyzed with univariate and multivariate Cox regression models based on preoperative and operative factors. Predictors included year of surgery, 1992 AJCC pathological stage, and surgical margin status.

Table 1: Demographics and pathologic and clinical outcomes.

| Characteristic | No. (IQR) |
|---|---|
| Median followup in years | 8.2 (4.5–12.5) |
| Median age in years | 65 (61–69) |
| Median pre-op PSA | 9.7 (6.1–13.4) |
| Pathologic tumor volume | 5.3 (3.0–12.0) |
| Pathologic Gleason sum | No. (%) |
| Gleason 8 | 68 (74.7) |
| Gleason 9 | 22 (24.2) |
| Gleason 10 | 1 (1.1) |
| Pathologic stage | |
| pT2 | 28 (31.1) |
| pT3/4 | 62 (68.9) |
| Positive margins | 48 (52.7) |
| Lymph node dissection and node status | |
| Nx | 34 (37.4) |
| N0 | 49 (53.8) |
| N1 | 6 (6.6) |
| N2 | 2 (2.2) |
| Adjuvant radiation | 10 (11.0) |
| Salvage radiation | 10 (11.0) |
| Neoadjuvant ADT | 9 (9.9) |
| Salvage ADT | 19 (20.9) |
| Biochemical recurrence | 33 (36.3) |
| Metastatic disease | 8(8.8) |
| PCSM | 9 (9.9) |
| Total no. patients | 91 (100) |

ADT: androgen deprivation therapy.

Actuarial analyses addressed the outcomes of PSA recurrence, distant recurrence, PCSS, and overall survival. In analyses of PCSS, patients without evidence of progression were censored at the time of last followup. A biochemical recurrence event for the purposes of Kaplan-Meier analysis was defined as a PSA of 0.1 ng/mL or the delivery of radiotherapy or hormonal therapy after later than 6 months after surgery. Kaplan-All statistical tests and figures were performed with S-PSS (2009) and statistical significance was set at 0.05.

Patients who died of other causes were censored at time of death. PSA recurrence-free data were censored if radiotherapy and/or hormonal therapy were delivered before PSA recurrence.

## 3. Results

Clinical and pathologic characteristics are shown in Table 1. The median followup was 8.2 years (interquartile range [IQR]: 4.5–12.5 years). The median age of the 91 person cohort was 65 years (IQR: 61–69 years) and the median PSA was 9.7 ng/mL (IQR: 6.1–13.4). At time of pathological analysis after RP, 62 (68.9%) had stage T3 disease or higher, 23 (25.3%) had pathologic Gleason 9 or higher, and 48 (52.7%) had a positive surgical margin.

Table 2: Binary logistic regression for prostate cancer-specific mortality.

| Characteristics | Univariate hazard ratio (95% CI) | ($P$ value) | Multivariate hazard ratio (95% CI) | ($P$ value) |
|---|---|---|---|---|
| Pre-op PSA | 1.038 (0.970–1.112) | 0.278 | 1.042 (0.953–1.139) | 0.366 |
| Gleason (8 versus 9–10) | 0.830 (0.160–4.312) | 0.825 | 1.087 (0.106–11.146) | 0.944 |
| Stage (pT3/4 versus pT2) | 4.000 (0.476–33.645) | 0.202 | 0.627 (0.032–12.429) | 0.759 |
| Margin status | 1.905 (0.446–8.136) | 0.384 | 4.943 (0.342–71.440) | 0.241 |
| XRT received | 1.912 (0.433–8.442) | 0.392 | 3.529 (0.356–34.987) | 0.281 |
| ADT received | 3.207 (0.790–13.007) | 0.103 | 0.703 (0.050–9.948) | 0.795 |
| Node status | 1.257 (0.127–12.419) | 0.845 | 2.127 (0.059–77.249) | 0.680 |

XRT = adjuvant or salvage radiotherapy; ADT: hormone use for relapse.

Table 3: Kaplan-Meier actuarial estimates of BCR-free survival, metastases-free survival, overall survival, and prostate cancer specific survival (PCSS).

| Cohort | Overall cohort | pT2/margin − | pT3 or margin + | pT3 & margin + |
|---|---|---|---|---|
| No at risk/5-year BCR-free survival (CI) | 90/0.69 (0.064–0.74) | 22/0.84 (0.76–0.90) | 25/0.65 (0.55–0.75) | 42/0.64 (0.56–0.68) |
| No at risk/5-year mets-free survival (CI) | 90/0.94 (0.91–0.97) | 22/1.00 (1.00–1.00) | 25/0.96 (0.92–1.00) | 42/0.89 (0.84–0.94) |
| No at risk/5-year overall survival (CI) | 90/0.96 (0.94–0.98) | 22/1.00 (1.00–1.00) | 25/1.00 (1.00–1.00) | 42/0.92 (0.88–0.96) |
| No at risk/5-year PCSS (CI) | 90/0.97 (0.95–0.99) | 22/1.00 (1.00-1.00) | 25/1.00 (1.00-1.00) | 42/0.95 (0.91–0.99) |
| No at risk/10-year BCR-free survival (CI) | 47/0.59 (0.53–0.65) | 13/0.77 (0.66–0.88) | 13/0.65 (0.55–0.75) | 21/0.47 (0.38–0.56) |
| No at risk/10-year mets-free survival (CI) | 61/0.88 (0.84–0.92) | 16/1.00 (1.00-1.00) | 19/0.96 (0.92–1.00) | 26/0.77 (0.69–0.85) |
| No at risk/10-year overall survival (CI) | 65/0.84 (0.79–0.89) | 16/0.85 (0.75–0.95) | 20/0.83 (0.74–0.92) | 29/0.85 (0.79–0.91) |
| No at risk/10-year PCSS (CI) | 65/0.94 (0.91–0.97) | 16/1.00 (1.00-1.00) | 20/0.88 (0.80–0.96) | 29/0.95 (0.91–0.99) |
| No at risk/15-year BCR-free survival (CI) | 29/0.52 (0.45–0.59) | 8/0.77 (0.66–0.88) | 9/0.45 (0.31–0.59) | 12/0.47 (0.38–0.56) |
| No at risk/15-year mets-free survival (CI) | 37/0.88 (0.84–0.92) | 9/1.00 (1.00-1.00) | 12/0.96 (0.92–1.00) | 16/0.77 (0.69–0.85) |
| No at risk/15-year overall survival (CI) | 40/0.69 (0.62–0.76) | 9/0.85 (0.75–0.95) | 12/0.74 (0.62–0.86) | 19/0.59 (0.48–0.70) |
| No at risk/15-year PCSS (CI) | 40/0.80 (0.73–0.87) | 9/1.00 (1.00-1.00) | 12/0.78 (0.66–0.90) | 19/0.73 (0.62–0.84) |

Table 2 shows the univariate and multivariate Cox regression model predicting prostate cancer-specific mortality. On both univariate and multivariate analysis, none of predictors remained statistically significant ($P > 0.05$).

Figure 1 graphically displays Kaplan-Meier estimates of BCR (a), metastases (b), overall survival (c), and PCSS (d) stratified by pathologic stage and surgical margin status. There was a trend for mean times to BCR ($P = 0.081$), and metastatic disease ($P = 0.060$), to be different between pT2/margin negative patients and pT3/margin positive patients.

Table 3 provides Kaplan-Meier actuarial estimates for time to BCR, metastases, overall survival and PCSS. Of all patients, the predicted 10-year BCR-free survival, mets-free survival, and PCSS were 59% (CI: 53%–65%), 88% (CI: 84%–92%), and 94% (CI: 91%–97%), respectively. Specifically, the predicted 10-year BCR-free rate was significantly better in those with organ-confined margin negative disease (pT2) than in those with locally advanced (pT3) margin positive disease (77% (CI: 66%–88%) versus 47%(CI: 38%–56%)). The predicted 15-year PCSS was significantly better in those with organ-confined margin negative disease (pT2) than in those with locally advanced (pT3) margin positive disease (100% (CI: 100%-100%) versus 73%(CI: 62%–84%)).

## 4. Discussion

We have demonstrated in a cohort with a median followup time of 8.2 years that cancer control is durable even 10 years after RP in those with pathologic high-grade disease. Although, 41% of patients developed BCR by 10 years, only 12% of patients in this extremely high-risk group progressed to distant metastases, and just 6% of patients actually died of their disease (Table 3).

When put into context, 59% of all patients with pathologic Gleason 8 disease or higher and 47% of patients with pathologic Gleason 8 disease or higher, pT3 stage and margin positive disease were cured of their disease (no BCR within 10 yr) with primary RP (Table 3). However, cure was not achieved solely with surgery. Of all patients, 11 received solely postoperative radiotherapy, 10 received long-term hormonal therapy, and 9 received both postoperative radiotherapy and long-term hormonal therapy. Clearly, this is a group of patients that will require multimodal therapy to achieve robust durable outcomes.

Our 10-year actuarial disease-specific mortality estimate (6%) was similar to other long-term RP series, including the UCLA group (8%) [20] and Hull et al. (2.4%) [21], and compares favorably with reports that have examined locally advanced disease specifically [12, 22].

It is intriguing that the classical predictors of outcome such as pathological stage and surgical margin status did not reach statistical significance in our multivariate analysis. However, the multivariate effect of these variables on PCSS was not assessed in most other long-term outcome series except that of Stephenson et al. [23]. However, stage was a significant predictor on multivariate analyses of BCR after

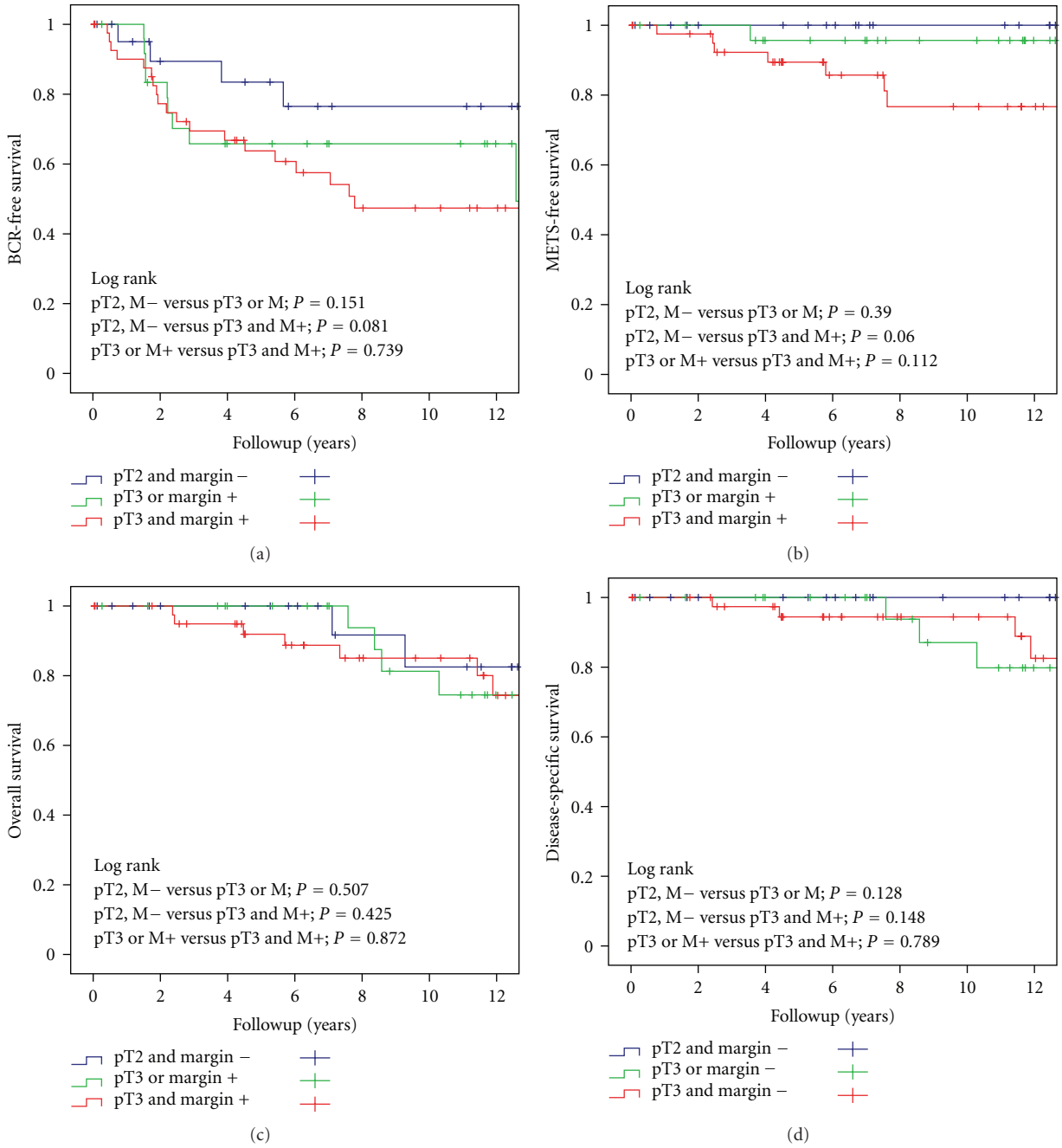


Figure 1: Kaplan-Meier estimates of BCR (a), distant recurrence (b), overall survival (c), and disease-specific survival (d) according to stage and surgical margin status.

RP in other series with long-term followup [19, 21] as was surgical margin status [21]. Thus, the positive predictor status of these classic variables with regard to BCR, but their inability to predict long-term PCSM suggest that they may not be important with regard to long-term oncologic control. This assumption will require further study in other long-term followup RP series.

The results of our study must be interpreted within the strengths and limitations of our study. First, our data derive from a single center over 20 years, and involve multiple surgeons. Thus, patient selection and surgical technique certainly differed and possibly may have introduced variation in outcome [24]. Moreover, patients underwent two surgical techniques, namely, RPP and RRP, which may have affected outcome. However, the literature suggests that there is no difference between RPP and RRP oncologic outcomes [25]. Second, we recognize that there is no centralized pathologic review and that therefore contemporary Gleason scores may well be ascribed a higher value [14]. However, all pathology was read at a single tertiary referral center

with a high level of GU pathology expertise. Moreover, we relied upon the original pathology report from VMMC to establish the histological differentiation. Gleason scores were not routinely recorded before 1992, and therefore, we relied upon the paradigm used by Roehl to assign Gleason scores to patients undergoing surgery before 1992 [19]. Finally, postoperative use of radiation and androgen deprivation therapy were given at the discretion of the treating physician and may have introduced substantial bias into the interpretation of the results.

## 5. Conclusions

In summary, we have demonstrated in a cohort with a median followup time of 8.2 years that cancer control is durable even 10 years after RP in those with pathologic Gleason 8–10 disease. Although, 41% of patients developed BCR by 10 years, only 12% of patients in this high-risk group progressed to metastases, and just 10% of patients died of their disease. Taken together, these long-term oncologic results support the use of RP for patients with high-risk localized prostate cancer.

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