
Prostate Cancer

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Abstract

The knowledge in the field of prostate cancer is rapidly changing. The majority of diagnoses relate to the use of screening prostate-specific antigen (PSA), which remains controversial. A combination of PSA level at diagnosis, clinical stage, and Gleason score is used to stratify patients into prognostic groups, with risk-adapted treatment assignment. The evaluation of treatment options for low-, intermediate- and high-risk prostate cancer has remained difficult primarily because of the lack of randomized trials. Most patients present with curative disease stage. Validated first-line treatment options include radical prostatectomy and radiation therapy, via either interstitial seed implants or external-beam radiation (EBRT). Radiation therapy for localized prostate cancer leads to equivalent oncologic outcomes as compared with radical prostatectomy. Interstitial seed implants and EBRT appear clinically equivalent. Modality-specific toxicity profile and logistics should be incorporated into the decision-making process of the individual patient. Results from randomized studies have established the value of dose-escalated radiotherapy alone in the unimodality setting versus standard-dose irradiation in combination with neoadjuvant and concurrent hormonal treatment. The timing and optimal duration of endocrine therapy in the era of dose escalation remain investigational. Adjuvant radiation therapy improves clinical outcome for pT3 prostate cancer or positive surgical margins.

Abbreviations

ADT	Androgen deprivation therapy
CTV	Clinical target volume
DVH	Dose volume histogram
EBRT	External beam radiotherapy
FFCF	Freedom from clinical failure

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GTV	Gross tumor volume
IMRT	Intensity modulated radiotherapy
IPSS	International prostatic symptom score
OS	Overall survival
OAR	Organ at risk
PCa	Prostate cancer
PFS	Progression free survival
PLND	Pelvic Lymph Node Dissection
PSA	Prostate specific antigen
PTV	Planning target volume
RT	Radiotherapy

1 Introduction

Cancer of the prostate (PCa) is currently the second most common cause of cancer death in men. The majority of diagnoses relate to the use of screening prostate-specific antigen (PSA), which remains controversial. PCa affects elderly men more often and therefore is a bigger health concern in developed countries. In developed countries, PCa accounts for 15 % of male cancers compared with 4 % of male cancers in developing countries. Within Europe large regional differences exist in the incidence rates of PCa (Brady et al. 2011; Heidenreich et al. 2011, 2012; Mottet et al. 2011).

Risk factors for prostate cancer are multiple. More established factors include increased life expectancy, routine adoption of PSA, ethnicity and family history. Potential but less established factors are obesity, dietary habits, exercise and prostatic inflammation.

Diagnosis and clinical staging depends on findings from history and physical examination, imaging and lab tests. Pathological staging depends on findings during surgical resection and pathological examination, in addition to those required in clinical staging. The 7th edition Union Internationale contre le Cancer (UICC) 2009 Tumour Node Metastasis (TNM) classification is used for staging (Table 1).

Beyond Gleason score, pretreatment serum PSA, and stage at diagnosis, additional pathologic factors including percent positive biopsy cores, PSA density and velocity, length of core involvement by tumor, and presence of perineural invasion also portend prognostic significance.

Since the clinical behavior of prostate cancer might range from indolent to highly aggressive, prognostic assessment is important for predicting outcome and treatment selection. A number of prognostic schemes have been developed. The clinical grouping system developed by the National Comprehensive Cancer Network (NCCN) is summarized, in addition with suggested general risk-

Table 1 Tumor node metastasis (TNM) classification of cancer of the prostate

<i>T—primary tumor</i>		
TX	Primary tumor cannot be assessed	
T0	No evidence of primary tumor	
T1	Clinically unapparent tumor not palpable or visible by imaging	
	T1a	Tumor incidental histological finding in 5 % or less of tissues resected
	T1b	Tumor incidental histological finding in more than 5 % of tissue resected
	T1c	Tumor identified by needle biopsy (e.g. because of elevated PSA level)
T2	Tumor confined within the prostate	
	T2a	Tumor involves one half of one lobe or less
	T2b	Tumor involves more than half of one lobe, but not both lobes
	T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule	
	T3a	Extracapsular extension (unilateral or bilateral)
	T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles. External sphincter, rectum, levator ani and/or pelvic wall	
<i>N—regional lymph nodes</i>		
NX	Regional lymph nodes cannot be assessed	
N0	No regional lymph node metastasis	
N1	Regional lymph node metastasis	
<i>M—distant metastasis</i>		
M0	No distant metastasis	
M1	Distant metastasis	
	M1a	Non-regional lymph node(s)
	M1b	Bone(s)
	M1c	Other site(s)

adapted treatment recommendations in Table 2. Localized prostate cancer can be treated with surgery, radiation therapy, or the combination of both. In addition, hormonal therapy plays a role in the treatment of locally advanced disease. For selected patients with very low- or low-risk disease, active surveillance may be a valid option. It should be noted that no randomized trial exists comparing modern radiation with prostatectomy techniques, and that oncologic outcomes for localized prostate cancer appear similar, when appropriate radiation doses are employed (Kupelian et al. 2004). In a recent large scale comprehensive review of the literature by Grimm et al. (2012) comparing risk stratified patients by treatment option and with long-term follow-up, the statistical analysis suggested that, in terms of biochemical-free progression, brachytherapy provides superior outcome in patients with low-risk disease. For intermediate-

Table 2 NCCN risk groups (2010)

Risk group	Parameter	Suggested treatment strategy
Very low	T1a, Gleason ≤ 6 , PSA < 10 , < 3 positive biopsy cores and < 50 % cancer per core	Active surveillance using PSA and DRE, if expected survival < 20 years
Low	T1–T2a, Gleason ≤ 6 and PSA < 10	Active surveillance using PSA and DRE if expected survival < 10 years, using PSA, DRE, and repeat biopsy if expected survival ≥ 10 years, or definitive therapy using IG-IMRT, brachytherapy, or radical prostatectomy (RP)
Intermediate	T2b–T2c, Gleason 7, or PSA 10–20	IG-IMRT with or without short-term ADT with or without brachytherapy boost or RP
High	T3a, Gleason 8–10, or PSA > 20	IG-IMRT and long-term ADT or radical prostatectomy plus PLND with or without adjuvant RT
Locally advanced: very high	T3b–T4	IG-IMRT plus long-term ADT or radical prostatectomy plus PLND with or without adjuvant RT or ADT
Locally advanced: LN	N1	ADT or IG-IMRT and long-term ADT
Distant metastases	M1	ADT

risk disease, the combination of EBRT and brachytherapy appears equivalent to brachytherapy alone. For high-risk patients combination therapies involving EBRT and brachytherapy plus or minus androgen deprivation therapy appear superior to more localized treatments such as seed implant alone, surgery alone or EBRT.

2 Treatment of Non-Metastatic Prostate Cancer

External-beam radiation therapy (EBRT) is one of the most important definitive treatment modalities for localized prostate cancer of all stages. Following initial single-institution reports of improved efficacy and therapeutic ratio by Hanks et al. (1998), dose-escalation strategies have become an important focus of prostate cancer research endeavors. Clinical evidence for dose escalation in EBRT is presented in Table 3 for randomized clinical trials.

Several randomized and non-randomized studies have shown that dose escalation with a dose-range of 76–80 Gy has a significant impact on 5-year survival without biochemical relapse. Two randomized trials focused on clinical stages T1–3 N0 M0 and opened the clinical decision for dose escalation. The MD Anderson study (Kuban et al. 2008) compared 78 with 70 Gy conventional radiotherapy. It included 305 patients stage T1b to T3 with a median follow-up of 8.7 years. The results showed a significant increase in freedom from biochemical and/or clinical failure ($p = 0.004$), which was largest for patients with initial PSA > 10 ng/ml ($p = 0.001$) (Table 3).

The PROG 95-09 study (Zietman et al. 2010) evaluated 393 T1b–T2b patients, of whom 75 % had a Gleason score < 6 and a PSA < 15 ng/ml. Patients were randomized

to receive an initial boost to the prostate alone, using conformal protons of either 19.8 or 28.8 Gy, and then 50.4 Gy to a larger volume. With a median follow-up of 5.5 years, there was a significant increase in 5-year freedom from biochemical failure ($p < 0.001$) in favour of low-risk patients given a higher dose (79.2 Gy) versus those given a conventional dose (70.2 Gy). There was a strong trend in the same direction for the intermediated-risk patients ($n = 144$, $p = 0.06$). 11 versus 6 % of patients subsequently required ADT for recurrence after conventional versus high-dose RT ($p = 0.047$). There remains no difference in OS (78.4 vs. 83.4 %, $p = 0.41$) and toxicity rates (1–3 % of grade 3–4) between the two arms.

A Dutch randomized phase III trial (Peeters et al. 2006) comparing 68 with 78 Gy showed a significant increase in 5-year freedom from clinical or biochemical failure (FFF or FFCF) for patients in an intermediate risk-group. 669 patients with T1b–T4 diseases were enrolled. With a follow-up of 51 months, 5-year FFF was significantly better after 78 Gy (64 vs. 54 %). No difference in late genitourinary or gastrointestinal toxicity was observed. As a result of these randomized studies, a minimum dose > 74 Gy is recommended for EBRT.

Androgen-deprivation therapy (ADT), consisting of a combination of luteinizing-hormone-releasing hormone (LHRH) suppression and an anti-androgen, has been evaluated as an adjunct to standard-dose EBRT as an alternative strategy to improve outcomes in patients with intermediate- and high-risk prostate cancer. The supportive trials, although heterogeneous in their patient selection criteria and radiation treatment volumes, generally demonstrate statistically and clinically significant improvements in overall survival. Evidence in support of androgen suppression is most mature in patients with high-risk disease.

Table 3 Main randomized studies on localized PCa supporting dose escalation

Reference	Number of patients	Dose escalation	Endpoint	Comment
Kuban et al. 2008	301	78 versus 70 Gy	↑ 8-year biochem. DFS: 78 versus 59 %	Largest benefit among patients with pretreatment PSA > 10 ng/ml
Peeters et al. 2006	669	78 versus 68 Gy	5-year FFF sign better after 78 Gy: 64 versus 54 %	No sign differences in FFCF or OS
Zietman et al. 2010	393	70.2 or 79.2 GyE proton RT	10-year ASTRO BF 32.4 versus 16.7 % for high-dose RT	Difference was largely due to low- and intermediate disease

Table 4 Main trials combining RT plus hormonal treatment (intermediate-risk prostate cancer)

Reference	Number of patients	Treatment schedule	Endpoint	Comment
D'Amico et al. 2008	206	70.35 Gy in 36 fractions \pm 6 months of ADT	All-cause mortality was sign greater in RT alone arm	Sign difference was primarily in patients with no or minimal comorbid illness
Denham et al. 2008	802	RT to 66 Gy alone or RT plus 3 or 6 months of ADT before and during RT	Sign improvement in PCa-specific mortality with 6 but not 3 months of ADT	

Beginning in the 1980s research organizations in the USA and Europe launched a series of trials for which mature follow-up data are now available, and which have systematically evaluated the efficacy, timing and duration of androgen suppression therapy. For overview of studies see Table 4.

Two randomized trials demonstrated clinical evidence on combined EBRT with hormonal therapy for intermediate-risk prostate cancer. D'Amico et al. reported on a phase III clinical trial comparing RT with or without 6 months of ADT. 80 % of 206 randomized patients had intermediate-risk prostate cancer (D'Amico et al. 2004, 2008). Conformal radiation comprised 70.35 Gy in 36 fractions prescribed to the prostate and seminal vesicles with a cone-down boost to the prostate. Initial results at a median follow-up of 4.5 years revealed statistical improvements in prostate cancer-specific survival, survival free of salvage androgen deprivation, and OS rate. Updated results after a median follow-up of 7.6 years showed that all-cause mortality was significantly greater in the RT alone arm (HR 1.8, $p = 0.01$). Subgroup analysis suggested that the significant difference was primarily in patients with no or minimal comorbid illness.

The TROG 96.01 randomized clinical trial (Trans-Tasman Radiation Oncology Group, Australia) studied the optimal duration of short-course hormonal therapy (Denham et al. 2008). This three-arm study compared prostate-only radiation to 66 Gy, versus radiation and 3 or 6 months of androgen deprivation before and during radiation for intermediate-risk patients. Results revealed a significant improvement in prostate-cancer-specific mortality with 6

(HR 0.56) but not 3 (HR 0.95) months of short-term androgen deprivation.

Fortunately, the incidence of locally advanced PCa (T3-4N0M0) has declined as a result of individual or mass screening. Pelvic lymph node irradiation is optional (see Sect. 3), but the results of radiotherapy alone are unsatisfactory. Because of the hormonal dependence of PCa, ADT has been combined with external irradiation in locally advanced PCa (T3-4N0M0) with the aim of reducing the risk of distant metastasis and decreasing the risk of non-sterilisation and/or local recurrence as a source of secondary metastases. Numerous randomized trials have confirmed the value of long-term administration.

The RTOG study 86-10 (Pilepich et al. 2001) included 471 patients with bulky ($>5 \times 5$ cm) tumours T2-4 N0-X M0. Androgen deprivation therapy was administered at 2 months before irradiation and during irradiation, or in the case of relapse in the control arm. 32 % of patients were diagnosed as T2, 70 % as T3-4, and 91 % as N0. The hormone treatment consisted of oral eulexine, 250 mg three times daily, and goserelin acetate (Zoladex) 3.6 mg every 4 weeks by subcutaneous injection. RT target volumes and doses were similar to RTOG 85-31 (Pilepich et al. 1997; Lawton et al. 2001), also including the regional lymphatics to an initial 44–46 Gy, followed by a prostate boost to 65–70 Gy. The 10-year overall survival estimates were 43 % for ADT plus irradiation versus 34 % for hormonal treatment, although the difference was not significant ($p = 0.12$). There was a significant improvement in the 10-year disease-specific mortality (23 vs. 36 %; $p = 0.01$), DFS (11 vs. 3 %; $p < 0.0001$) and in biochemical failure

(65 vs. 80 %; $p < 0.0001$). No significant impact on the risk of fatal cardiac events was seen with the addition of ADT.

The RTOG 85-31 trial (Pilepich et al. 1997; Pilepich et al. 2005; Lawton et al. 2001) randomized 977 patients to adjuvant goserelin (Arm I) versus observation (Arm II) with hormones initiated at relapse. Eligible patients had advanced tumor characteristics (T3-4 N0-1 M0) or pathologic penetration (pT3) through the capsule to the resection margin or seminal vesicle involvement after RP. Androgen deprivation therapy was begun in the last week of irradiation and continued up to relapse or was started at recurrence. A total of 15 % of patients in the first group and 29 % in the second group had undergone RP, 14 and 26 % were pN1. Goserelin was administered every 4 weeks. RT portals included treatment of the regional lymphatics to an initial 44–46 Gy (except in node-negative postoperative cases) followed by a prostate boost to 65–70 Gy. With a median follow-up of 7.6 years for all patients, at 10 years, the absolute survival rate was significantly greater for the adjuvant arm than for the control arm: 49 versus 39 % ($p = 0.002$). The 10-year local failure rate for the adjuvant arm was 23 versus 38 % for the control arm ($p < 0.0001$). The corresponding 10-year rates for the incidence of distant metastases and disease-specific mortality was 24 versus 39 % ($p < 0.001$) and 16 versus 22 % ($p = 0.0052$), respectively, both in favour of the adjuvant arm (Lawton et al. 2001, 2008; Pilepich et al. 2005).

The EORTC 22863 was an open-labeled randomized phase 3 trial (Bolla et al. 2002, 2010). Eligible patients were younger than 80 years and had newly diagnosed histologically proven T1–2 prostatic adenocarcinoma with WHO histological grade 3, or T3-4N0M0 and any histological grade. The trial compared EBRT and adjuvant long-term (concurrent and adjuvant) androgen suppression with radiotherapy alone. EBRT initially targeted the prostate and pelvic nodes to 50 Gy, with a subsequent prostate-only boost to an additional 20 Gy. Hormonal therapy consisted of monthly goserelin administration for 3 years, beginning on the first day of EBRT and 1 month of cyproterone acetate. With a median follow-up of 66 months, combination therapy compared with radiotherapy alone yielded significantly better survival (78 % vs. 62 %, $p = 0.001$) (Bolla et al. 2002). At a median follow-up of 9.1 years, the 10-year overall survival remained significantly higher at 58.1 versus 39.8 % ($p < 0.0001$), as did clinical progression-free survival at 47.7 versus 22.7 % ($p < 0.0001$). The 10-year cumulative incidence of PCa mortality was 11 versus 31 % ($p < 0.0001$). No significant difference in cardiovascular mortality was noted between treatment groups both in patients who had cardiovascular problems at study entry and in those who did not. The 10-year cumulative incidence of cardiovascular mortality was 11.1 versus 8.2 % ($p = 0.75$) (Bolla et al. 2010).

In conclusion the trials devoted to locally advanced PCa have shown a significant gain in overall survival of the combination of EBRT and long-term ADT and raised the question of whether the gain was due to ADT alone rather than to the combined approach. However, many trials were launched to assess the value of a long-term ADT plus or minus irradiation.

Mottet et al. (2012) report on the results of a phase 3 multicentric randomized trial devoted to 264 N0-X patients classified as cT3–4 ($n = 254$) or pT2 with positive biopsies of the capsule ($n = 10$), randomly allocated between long-term (3-year) ADT alone or combined with three-dimensional conformal radiotherapy (3D-CRT). ADT was administered with an LHRH-agonist (leuporelin) given subcutaneously with a 3-monthly depot and an oral anti-androgen (flutamide) for 1 month to inhibit flare-up. In the ADT alone arm, 33 patients received salvage RT for local progression. RT was focused on the pelvis with a four-field box technique (46 ± 2 Gy) followed by a boost on the prostate and periprostatic tissue (22 ± 2 Gy). The patients were <80 year old with a World Health Organization (WHO) performance score (PS) < 2. There was no pathologic central review. 49 % had Gleason score 4–6, and 22.5 % of the patients had a baseline PSA > 20 ng/ml. With a median follow-up of 67 months, there was a significant difference in favor of the combined approach with regard to local-regional control ($p < 0.0001$), metastatic progression ($p = 0.018$), and progression-free survival ($p < 0.001$), but there was no improvement in overall survival or disease-specific survival because of an insufficient target sample size and/or not mature enough results. With the same concept, a life-long ADT, and a greater target sample size, the trials reported by Warde et al. (2011) and Widmark et al. (2009) shared these results but with added value for survival.

Warde et al. (2011) reported on a cohort of 1205 N0-X patients (T3–4) ($n = 1057$), T2 with PSA > 40 ng/ml ($n = 119$), or T2 with PSA > 20 ng and Gleason > 8 ($n = 25$) randomized between life-long ADT (bilateral orchiectomy or LHRH agonist) with or without RT (65–70 Gy to prostate \pm 45 Gy to pelvic lymph nodes). With 6-year median follow-up, the combined approach significantly reduced the risk of death ($p = 0.033$) and of disease-specific death ($p = 0.001$). The SPCG-7/SFUO 3 trial (Widmark et al. 2009) accrued a cohort of 875 N0-X M0 patients (T3, any WHO grade ($n = 862$); T1b–T2 G2–3 ($n = 168$); unknown ($n = 5$)). Patients were randomly assigned to endocrine treatment alone (3 months of total androgen blockade followed by continuous endocrine treatment using flutamide) or to the same endocrine treatment combined with 3D-CRT (70 Gy to the prostate). With 7.6 years median follow-up, the combined approach halved the 10-year PCa-specific mortality ($p < 0.0001$) and

Table 5 Results of brachytherapy ($^{125}\text{I}/^{103}\text{Pd}$ -Isotopes)

Reference	Patients (n)	Risk group	EBRT	Endpoints (years)	Biochemical control (%)	Comment
Buckstein et al. 2013	131	Low and intermediate	Yes	11.5	All: 90	Patients younger than 60 years
Kao et al. 2008	643	Low	No	5	All: 97	Neoadjuvant hormonal treatment
Taira et al. 2010	463	Low and intermediate	No	12	All: 97	
Zelevsky et al. 2007	2693	All	No	8	Low: 82 Intermediate: 70 High: 48	Meta-analysis

decreased overall mortality ($p < 0.004$). These results mimic somehow what was observed for locally advanced breast cancer, with the greatest effect being achieved with the combination of RT and endocrine treatment given concomitantly.

3 Prophylactic Irradiation of Pelvic Lymph Nodes in High-Risk Localized PCa

The optimal strategy for target definition, especially whole-pelvis lymph nodes versus prostate-only radiation therapy, has not been determined. Invasion of the pelvic lymph nodes is a poor prognostic factor. However, randomized trials showed inconclusive results according to what extent patients benefited from prophylactic whole-pelvis irradiation. The RTOG 94-13 four-arm randomized trial (Roach et al. 2003) attempted to discern the relative merits of pelvic nodal irradiation versus prostate-only EBRT in patients with an estimated risk of lymph node involvement of 15 %, and timing (adjuvant versus neoadjuvant and concurrent) of hormonal therapy. The total duration of hormonal treatment was 4 months. An OS difference was seen among all study groups, yet there were no significant differences in PFS or OS between neoadjuvant versus adjuvant hormones, or pelvis versus prostate-only radiation. When neoadjuvant hormone therapy was used in conjunction with EBRT, pelvic nodal irradiation yielded an improved PFS versus prostate-only RT. Neoadjuvant hormones plus pelvic nodal RT improved OS versus adjuvant hormones plus pelvic nodal RT. Late severe GU toxicities were similar in the 4 arms, though severe GI toxicities were more frequent in the neoadjuvant hormone and whole-pelvis arm.

The GETUG-01 randomized phase III trial (Pommier et al. 2007) also studied the role of pelvic and prostate versus prostate-only RT. The trial stratified patients according to risk of lymph node involvement. Initial results with limited follow-up of 42 months demonstrated no significant difference in 5-year PFS between the study groups, either in the high- or low-risk strata.

4 Transperineal Brachytherapy

Transperineal brachytherapy is a safe and effective technique. Modern series continue to demonstrate excellent outcomes for radioactive implantation, either as monotherapy for low-risk cases or selected high-risk patients, or as boost treatment in conjunction with external beam therapy. According to the American Brachytherapy Society there is consensus on the following eligibility criteria: Stage cT1b–T2a N0 M0, a Gleason score ≤ 6 assessed on a sufficient number of random biopsies, an initial PSA level of <10 ng/ml, <50 % of biopsy cores involved with cancer, a prostate volume of <50 cm³, an International Prostatic Symptom Score ≤ 12 (IPPS) (Nag et al. 1999).

There are no randomized trials comparing brachytherapy with other curative treatment modalities, and outcomes are based on non-randomized case series. Results of permanent implants have been reported from different institutions, with different follow-up. Biochemical control was reported to range from 48 (high risk) to 97 % (low risk) (see Table 5). A significant correlation has been shown between the implant dose and recurrence rates. As demonstrated in a recent multi-institutional study of 2693 men with T1–2 prostate cancer, D90 > 130 Gy emerged as a highly significant predictor of 8-year PSA relapse-free survival (93 vs. 76 %, $p < 0.001$).

5 Immediate and Delayed Post-Operative External Irradiation After Radical Prostatectomy

While prostatectomy provides good control rates for patients with organ-confined disease, failure rates for patients with cancer extensions beyond the capsule are substantial, particularly in cases of high Gleason grade and positive margins. Extracapsular invasion (pT3) is associated with a risk of local recurrence, which can be as high as 30 %. In multifactorial analyses, the predictors of biochemical relapse

are: PSA level ($p = 0.005$), Gleason score of the surgical specimen ($p = 0.002$) and positive surgical margins ($p < 0.001$).

Three prospective randomized trials have assessed the role of immediate post-operative radiotherapy (adjuvant radiotherapy). The randomized phase III EORTC trial 22911 (Bolla et al. 2012) recruited patients age 75 or younger with untreated cT0–3 PCa. Eligible patients were randomly assigned centrally (1:1) to postoperative irradiation (60 Gy) to the surgical bed or to a wait-and-see policy until biochemical progression (increase in PSA $> 0.2 \mu\text{g/L}$ confirmed twice at least 2 weeks apart). 1,005 patients were randomly assigned and were followed up for a median of 10.6 years. Postoperative irradiation significantly improved biochemical progression-free survival compared with the wait-and-see group (198 [39.4 %] of 502 patients in postoperative irradiation group vs. 311 [61.8 %] of 503 patients in the wait-and-see group had biochemical or clinical progression or died; HR 0.49 [95 %, CI 0.41–0.59]; $p < 0.0001$). Late adverse effects (any type of any grade) were more frequent in the postoperative irradiation group than in the wait-and-see-group (10-year cumulative incidence 70.8 % [66.6–75.0] vs. 59.7 % [55.3–64.1]; $p = 0.001$). It was concluded that results at median follow-up of 10.6 years show that conventional postoperative RT significantly improved survival and local control compared with a wait-and-see policy, supporting results at 5 year follow up; however, improvements in clinical progression-free survival were not maintained. Exploratory analyses suggested that postoperative RT might improve clinical progression-free survival in patients younger than 70 years and in those with positive surgical margins, but could have a detrimental effect in patients aged 70 years or older.

The most suitable candidates for immediate radiation therapy might therefore be those with multifocal positive surgical margins and a Gleason score > 7 . The conclusion of the ARO trial 96-02 ($n = 385$) appear to support those of the EORTC study (Wiegel et al. 2009). In this phase III trial patients with pT3N0 disease and (in contrast to the other two studies) an undetectable PSA level after RP were randomized to adjuvant RT (60 Gy) versus observation. After a median follow-up of 54 months, the irradiated group demonstrated a significant improvement in biochemical progression-free survival of 72 versus 54 %, respectively ($p = 0.0015$). This finding demonstrates that adjuvant radiotherapy works even in the setting of undetectable PSA after RP and additional risk factors.

Between 1988 and 1997, SWOG 8794 randomized 425 men with non-organ-confined cancer or positive surgical margins (pT2+N0M0 or pT3N0M0) to immediate adjuvant RT using 60–64 Gy by conventional technique versus observation (Thompson et al. 2009). Because the study did not require men to have an undetectable PSA prior to study

entry, 33 % of men in both arms had PSA $> 0.2 \text{ ng/ml}$ at the time of randomization. The use of salvage RT was not mandated by protocol in the observation arm, and a total of 70 men (33 %) ultimately received postoperative RT (most for a rising PSA). The median PSA at the time of salvage RT in these men was 1.0 ng/ml, which would be considered “late” salvage therapy by current standards. Over a median follow-up of almost 13 years, adjuvant RT was associated with a significant improvement in metastasis-free survival (HR: 0.7, $p = 0.016$) and overall survival (HR: 0.7, $p = 0.023$). Metastases-free survival considers the development of distant metastasis and death from any cause as events. The rate of observed distant metastasis was low (17 % in the observation arm and 9 % in the RT arm), and the majority of events in the analysis of metastasis-free survival and OS were deaths without evidence of metastatic PCa (68 % in the observation arm and 78 % in the RT arm). Adjuvant RT was also associated with reductions in the need of salvage RT. In exploratory analyses, all subgroups (Gleason 2–6 vs. 7–10, pT3a or postoperative surgical margins vs. seminal vesicle invasion, undetectable vs. detectable PSA) appeared to benefit from adjuvant RT with respect to metastasis-free survival. Rectal and urinary toxicity and urethral stricture rates were higher with adjuvant RT, but the overall rates were low.

In conclusion, the decision whether to proceed with adjuvant RT for high-risk PCA (pT3–4 pN0–1) after RP or to postpone RT as an early salvage procedure in case of biochemical relapse remains difficult. In daily practice, the urologist should explain to the patient before RP that adjuvant irradiation could be applied if the patient has negative prognostic risk factors. Ultimately, the decision to treat needs a multidisciplinary approach to determine the optimal timing of radiotherapy when used and to provide justification when not used.

6 The Role of Hypofractionation

In ideal circumstances, the fractionation schedule of radiotherapy should match the fractionation sensitivity of the tumor relative to nearby normal tissues. The alpha-beta (α/β) ratio for most cancers is believed to be about 10 Gy, but for prostate cancer values as low as 1.5 Gy have been suggested, which is smaller than the roughly 3 Gy reported for the late reactions of most normal tissues (including rectum). These findings have potentially important therapeutic implications. Hypofractionated radiotherapy with fewer high-fraction-size treatments would be beneficial for prostate cancer because it would deliver a larger biological-equivalent dose to the tumor than would conventional treatment in 1.8–2.0 Gy fractions, while maintaining a similar or lower incidence of late normal tissue reactions.

Furthermore, improved resource utilization and patient convenience because of short treatment duration would be important gains. Maintenance of few treatment-related side-effects is of paramount importance.

Dearnaley et al. (2012) undertook a multistage, multicenter randomized controlled trial (Conventional or Hypofractionated High-dose Intensity Modulated Radiotherapy in Prostate Cancer: CHHiP). Men with localized prostate cancer were randomized between 2002 and 2006 at 11 UK centres. Patients were randomly assigned in a 1:1:1 ratio to receive conventional or hypofractionated high-dose intensity modulated radiotherapy, and all were given 3–6 months of neoadjuvant androgen suppression. Computer-generated random permuted blocks were used, with risk of seminal vesicle involvement and radiotherapy-treatment centre as stratification factors. The conventional schedule was 37 fractions of 2 Gy to a total dose of 74 Gy. The two hypofractionated schedules involved 3 Gy treatments given either in 20 fractions to a total dose of 60 Gy, or 19 fractions to a total of 57 Gy. The primary endpoint was proportion of patients with grade 2 or worse toxicity at 2 years on the RTOG scale. The primary analysis included all patients who received at least one fraction of radiotherapy and completed a 2-year assessment. 153 men recruited to stages 1 and 2 were randomly assigned to receive conventional treatment of 74 Gy, 153 to receive 60 Gy, and 151 to receive 57 Gy. With 50.5 months median follow-up 4.3 % (95 % CI 1.6–9.2) of 138 men in the 74 Gy group had bowel toxicity of grade 2 or worse on the RTOG scale at 2 years, as did 3.6 % (1.2–8.3) of 136 men in the 60 Gy group, and 1.4 % (0.2–5.0) of 143 men in the 57 Gy group. For bladder toxicities 2.2 % (0.5–6.2) of 138 men, 2.2 % (0.5–6.3) of 137, and 0.0 % (0.0–2.6) of 143 had scores of grade 2 or worse on the RTOG scale at 2 years. From these results it was concluded that hypofractionated high-dose radiotherapy seems equally well tolerated as conventionally fractionated treatment at 2 years.

In a recent publication by Botrel et al. (2013) a systematic review and meta-analysis of all randomized controlled trials comparing the efficacy and side effect profile of hypofractionated versus conventional EBRT for PCa was conducted. The final analysis included nine trials comprising 2,702 patients. Freedom from biochemical failure was reported in only three studies and was similar in patients who received hypofractionated or conventional radiotherapy. The incidence of acute adverse gastrointestinal events was higher in the hypofractionated group. Acute genitourinary toxicity was similar among the groups. The incidence of all late adverse events was the same in both groups. Hypofractionated radiotherapy in localized prostate cancer was not superior to conventional radiotherapy and showed higher acute gastrointestinal toxicity in this meta-analysis. Because the number of published studies is still

small, future assessments should be conducted to clarify better the true role of hypofractionated radiotherapy in patients with prostate cancer.

7 Radiation Therapy Techniques and Target Delineation

IMRT represents the current standard of care for prostate EBRT. According to patient set up and planning, patients should be instructed to present with an empty rectum and comfortably full bladder. Patients are positioned either supine or prone (with or without a rectal balloon depending on institutional practice) on a custom immobilization device. A volumetric CT scan employing a slice thickness < 3 mm is obtained through the volume of interest and imported into a computer for organ segmentation and treatment planning. MRI fusion is employed to delineate the prostate apex. MRI fusion enhances definition of the prostate-rectum interface, the prostatic apex, and neurovascular bundles. The use of a T2-weighted volumetric sequence is suggested. Given susceptibilities for organ deformation, intra- and interfraction organ motion, IMRT is typically combined with daily image guidance. A variety of methods, including ultrasound, fiducial implantation and KV imaging, KV cone-beam CT, MVCT, and intrafraction tracking using transponders are in clinical use. Pelvic radiation using IG-IMRT and incorporating intraprostatic fiducial markers can reduce the volumes of rectum and bladder receiving high doses, thus reducing toxicities. The recently published RTOG consensus documents represent a valuable guideline for postoperative target delineation (Lawton et al. 2009; Michalski et al. 2010). Definitions of gross target volume (GTV), clinical target volume (CTV), and planning target volume (PTV) in IMRT in prostate-only radiation include prostate on imaging studies as GTV, with 0.5–1 cm margins in 3D to achieve PTV. The CTV of seminal vesicles and pelvic lymph node regions (if select to treat) include distal common, internal, and external iliac regions, presacral, and obturator regions. The probability of involvement can be determined by stage, pretreatment PSA, PSA doubling time and/or velocity, high-percent biopsy core involvement, the presence of perineural invasion, and the Roach formulas and/or Partin tables (Roach et al. 1994; Partin et al. 1997; Eifler et al. 2013). These and different nomograms are available on the internet, for example via CaP Calculator. Using a nationally representative mail survey of 1,422 prostate cancer specialists in the United States, Kim et al. queried about self-reported clinical implementation of quality of life instruments, prostate cancer nomograms and life expectancy prediction tools in late 2011. A total of 313 radiation oncologists and 328 urologists completed the survey for a 45 % response rate. Although 55 % of

respondents reported using prostate cancer nomograms, only 27 and 23 % reported using quality of life and life expectancy prediction instruments, respectively (Kim et al. 2012). Probably, these variations result from different factors, including time constraints and unresolved issues around the validity of different tools and their applicability in different patient populations, as discussed in the introductory chapters of this textbook. Organs at risk (OARs) in EBRT of prostate cancer, in both adjuvant and definitive settings, include rectum and bladder. Suggested DVH constraints for dose-escalated IMRT are specified in the RTOG active protocols. Efforts towards development of toxicity-prediction nomograms are ongoing (Fiorino et al. 2012; Roeloffzen et al. 2012; Valdagni et al. 2012).

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