External beam radiotherapy for localized prostate cancer

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Radiotherapy (XRT) is a curative treatment option for prostate cancer (PCa). Recent XRT technologies allow higher dose therapy that lead to increased local control with less adjacent tissue damage. Additionally, receiving neo-adjuvant or adjuvant hormonotherapy (HT) during radiation therapy increases the curative effect. The aim of this paper is to review the current literature and guidelines on external beam radiation therapy for PCa. However, brachytherapy and radiosurgery, a recently evolving relatively new technology for the radiotherapeutic management of localized PCa, are beyond the scope of this paper.

PATIENT SELECTION
Clinicians should consider some important information about the patient before recommending any treatment option for PCa. These are the stage of the disease (staging accordingly 2009 TNM classification), the Gleason score, the level of prostate-specific antigen, general health status of the patient (age, patient’s comorbidity, life expectancy, quality of life), infravesical obstructive status of the patient (international prostate symptom score and uroflowmetry recordings), and the risk status of the patient (National Comprehensive Cancer Network¹ and/or D’Amico prognostic factor classification²).

Patient comorbidity can be evaluated with Charlson score.²³ Comorbidity is the major predictor of mortality; at 10 years, most men with Charlson score ≥2 died from competing causes irrespective of age or tumor aggressiveness. Albertsen et al. evaluated a total of 19,639 patients with clinically localized PCa regarding comorbidity-specific survival.³ They found that for men with clinic stage T1c and Gleason score 5 to 7, the overall 5-year mortality rate raised from 11.7% to 42.5%, and the overall 10-year mortality rate raised from 28.8% to 83.1% as the Charlson score at diagnosis increases from zero to two or more. In contrast, these men had 5- and 10-year prostate cancer-specific mortality rates of 1.6% to 4.3% and 4.8% to 5.3%, respectively.⁵

Some risk classifications (Table 1) can be used to stratify patients by the risk of biochemical failure after curative therapy. These risk groups are used to select the appropriate options that should be considered for treatment. According to these classifications, the rate of PCa-specific mortality is very high in the high-risk group while very low at the low-risk group. On the other hand, the addition of neo-adjuvant or adjuvant HT to curative treatment is also selected according to these classifications.

DOSE ESCALATED RADIOTHERAPY
Therapeutic radiation can be delivered with multiple techniques. The main goal of XRT is to reach the maximum radiation dose at the target organ with less adjacent tissue damage. Because the prostate is influenced by both bowel and bladder filling, and thus mobile within the pelvis, the conventional XRT had larger planning margin that leads to underdosing of the target and overdosing of surrounding normal tissues. Consequently, three-dimensional conformal radiotherapy (3D-CRT) and intensity modulated external-beam radiotherapy (IMRT) technics were developed for the high-dose treatment of PCa.

In 3D-CRT, the patient is scanned at the treatment position, and three-dimensional images of the target tissue are obtained with 5 mm surrounding safety margin. Real-time verification of the irradiation field leads to correct the deviations where displacement is more than 5 mm. IMRT has multileaf collimators and specific software. Multileaf collimator automatically adapts to the contours of the target volume seen by each beam. This allows for a more complex distribution of the dose to be delivered within the treatment field and provides concave isodose curves. Thus, adjacent tissues are preserved with sharply estimated margins. Both European Association of Urology (EAU) and NCCN guidelines recommended image guided radiation therapy with either 3D-CRT or IMRT for target margin reduction and treatment accuracy.¹⁶ However, to date, no randomized trials have been published comparing dose escalation using IMRT and 3D-CRT. EAU PCa guideline recommended image guided XRT with or without IMRT in localized prostate cancer (T1c-T2c N0 M0) even for young patients who decline surgical intervention.⁷

There is strong evidence that increasing radiation dose has a substantial positive effect on biochemical control.⁷⁻¹¹ Dose escalation studies are summarized in Table 2. Peeters et al. randomized 664 patients into 68 Gy versus 78 Gy groups in Dutch trial.⁷ Although about half of them were high-risk patients and 143 of them received HT, they found that 78 Gy arm had significantly better biochemical failure (BF) rate compared to 68 Gy (hazard ratio of 0.74, P = 0.02). However, they did not find any significant difference regarding clinical failure (local or regional relapse, metastasis exc.) or overall survival (OS).

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Dearnaile et al. published the MRC-RTO1 trial that compared standard 64 Gy versus 74 Gy XRT. All patients had neo-adjunct HT. They randomized 843 patients and 61% of them had Gleason score <7. They found biochemical progression-free survival (bPFS) of 71% in 74 Gy patients compared to 60% in 64 Gy at 5 years. However, 74 Gy group had 33% late bowel toxicity compared to 24% in the 64 Gy group within 5 years.

Zietman et al. compared 70.2 Gy to 79.2 Gy in PROG 95-09 trial. A total of 393 men were randomly assigned, and median follow-up was 8.9 years. Although 85% of the patients had PSA ≤10 ng ml⁻¹, they found high-dose XRT less likely to have local failure (hazard ratio of 0.57) and BF (32.4% vs 16.7%, P < 0.0001). When they examined only low-risk patients, BF rates were found 28.2% versus 7.1%, respectively. However, no significant difference was found in the intermediate-risk group regarding to BF (42.1% vs 30.4%, P = 0.06). They also found no difference in the OS rates.

Kuban et al. compared 70 Gy versus 78 Gy in the MD Anderson study. They analyzed 301 patients; 70% of them were intermediate-risk and 30% were high-risk. They found that patients with pretreatment PSA >10 ng ml⁻¹ or high-risk disease had higher biochemical and clinical failures when treated with 70 Gy. At 10 years after treatment, 16% of high-risk patients treated with 70 Gy had died of disease as compared with 4% of patients treated with 78 Gy (P = 0.05). They found no significant difference in low-risk patients.

Beckendorf et al. also compared 80 Gy versus 70 Gy without HT in GETUG study. They found BF within 5 years were 28% versus 16.7%, respectively (P = 0.036). Their subgroup analysis showed a better biochemical outcome for the higher dose group with an initial PSA >15 ng ml⁻¹. The toxicity results were found to be similar in both 70 Gy and 80 Gy group.

Also Zelefsky et al. published a retrospective analysis of 2551 patients to identify predictors of biochemical tumor-control and distant metastases-free survival (DMFS) outcomes for patients with clinically localized PCa treated with XRT. Of those 49% received HT. Median follow-up was 8 years, extending over 20 years. Prescribed doses ranged from 64.8 to 86.4 Gy. They found that higher radiation dose was one of the most important predictors of long-term biochemical tumor-control and improved PSA relapse-free survival (PSA-RFS) outcomes in all risk groups. In addition, they found that the use of androgen deprivation therapy (ADT), especially in intermediate- and high-risk patients, was associated with significantly improved biochemical tumor-control outcomes.

In conclusion, although study outcomes differ regarding HT utilization and the risk group of patients, higher dose XRT had a better outcome than standard dose with comparable toxicity rates. However, to date, no trials have shown that dose escalation results in an OS benefit. NCCN recommended highly conformal XRT techniques for the treatment of PCa. Doses of 75.6 to 79.2 Gy in conventional fractions to the prostate are appropriate for low-risk patients. For patients with intermediate- or high-risk disease, doses

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### Table 1: Prostate cancer progression risk classification

| Risk Category | Very low-risk | Low-risk | Intermediate-risk | High-risk | Very high-risk |
|---------------|---------------|----------|-------------------|-----------|---------------|
| D’Amico (AUA) | −             | PSA <10 ng ml⁻¹, and GS <7, or cT1–2a | PSA >20 ng ml⁻¹, or GS >7, or cT2b | PSA >20 ng ml⁻¹, or GS >7, or cT2c–3a | − |
| NCCN          | cT1c, GS <7, PSA <10 ng ml⁻¹, PSAD ≤0.15, ≤3 positive biopsies | PSA >10–20 ng ml⁻¹, or GS >7, or cT2b–2c | PSA >20 ng ml⁻¹, or GS >7, or cT3a | PSA >20 ng ml⁻¹, or GS >10, or ≥cT3a | − |
| EAU           | −             | PSA <10 ng ml⁻¹, and GS <7, or cT1c | PSA >10–20 ng ml⁻¹, or GS >7, or cT2b–2c | PSA >20 ng ml⁻¹, or GS >8, or ≥cT3a | − |

PSA: prostate-specific antigen; PSAD: prostate-specific antigen density; GS: Gleason score; EAU: European Association of Urology; NCCN: National Comprehensive Cancer Network; AUA: American Urological Association

### Table 2: Dose escalation studies

| Study (reference) | Year | n | Included patients | Dose | Median follow-up | Results (LD vs ED) |
|-------------------|------|---|-------------------|------|-----------------|-------------------|
| MDA study[^15]    | 2011 | 301 | Intermediate-risk 70% High-risk 30% | 70 versus 78 | 9 years | CSS High-risk: 86% versus 96% PSA >10; 85% versus 98% BF 32.4% versus 16.7% |
| PROG 95-09[^9]    | 2010 | 393 | T1b–T2 100% PSA ≤10; 85% PSA 10–15; 15% GS <7; 75% Intermediate-risk 37% High-risk 4% | 70.2 versus 79.2 | 8.9 years | BF 32.4% versus 16.7% |
| MRC RTO1[^4]      | 2007 | 843 | T1b–T2 83% PSA ≤10; 35% PSA >20; 26% GS <7; 61% ADT (neo)+ | 64 versus 74 | 5.2 years | bPFS 60% versus 71% |
| Dutch study[^9]   | 2006 | 664 | T1–T2 64% T3 37% PSA ≤10; 39% PSA >20; 24% Intermediate-risk 28% High-risk 54% ADT + for 143 patients | 68 versus 78 | 4.2 years | BF 36% versus 26% |
| GETUG 06[^11]     | 2011 | 306 | LNI risk of <10% (Partin) or pN0 No hormonal therapy Before, during, or after radiotherapy | 70 versus 80 | 5.1 years | BF 39% versus 28% |

LD: low dose; ED: escalated dose; CSS: cancer-specific survival; bPFS: biochemical progression-free survival; LNI: lymph node involvement; GS: gleason score; ADT: androgen deprivation therapy; PSA: prostate-specific antigen; BF: biochemical failure
up to 81.0 Gy provide improved PSA-assessed disease control.  

**ROLE OF ANDROGEN DEPRIVATION THERAPY**

Androgens are important mitogens in prostate cancer in all phases of the disease.  

The addition of ADT to XRT improves biochemical and survival outcomes in patients with locally advanced disease or with poor risk factors.  

The studies comparing XRT with or without ADT are given in Table 3.

Pilepich et al. designed a study (RTOG 85-31) to evaluate the effectiveness of adjuvant androgen suppression.  

Eligible patients were those with palpable primary tumor extending beyond the prostate (clinical stage T3) or those with regional lymphatic involvement. The adjuvant ADT was administered (starting during the last week of XRT) in arm I and at the time of relapse in arm II. Administration of the drug was to continue indefinitely or until the sign of disease progression. They found that at 10 years, the absolute survival rate was significantly greater for the adjuvant arm than for the control arm: 49% versus 39%, respectively ($P = 0.002$), and the corresponding 10-year disease-specific mortality was 16% versus 22% ($P = 0.0052$), respectively.

Bolla et al. published a study (EORTC 22863) to evaluate the impact of ADT in 415 patients.  

About 90% of them had T3–4 disease. The ADT was started at the first day of pelvic irradiation and continued for 3 years. When XRT alone was compared to XRT plus ADT, they found that at 10 years clinical disease-free survival was 22.7% versus 47.7%, OS was 39.8% versus 58.1%, and prostate-cancer mortality was 30.4% versus 10.3%, respectively.

Also Jones et al. studied (RTOG 94-08) the impact of the short-term ADT in localized PCa patients.  

They randomly assigned patients with stage T1b–T2b and a PSA level of 20 ng ml$^{-1}$ or less to XRT alone or XRT with 4 months of ADT, starting 2 months before XRT. They found the 10-year rate of OS was 62% in XRT plus ADT group and 57% in XRT alone group. They also found that the addition of short-term ADT was associated with a significant decrease in the 10-year disease-specific mortality from 8% to 4%. Another question of interest is the duration of ADT in combination with XRT. The issue was studied in several phase III trials and they are summarized in Table 4. Hanks et al. designed a study (RTOG 92-02) to evaluate the impact of long-term ADT. All patients received 4 months of ADT, starting 2 months before XRT. Then patients were randomly assigned to no other treatment or 24 months additional ADT. They found that long-term ADT resulted in significantly better cancer-specific survival and disease-free survival than short-term ADT (94.6% vs 91.2%; 46.4% vs 28.1%, respectively). They also found that OS rates were significantly better in the Gleason score > 7 subgroup.

Bolla et al. published another study (EORTC 22961) for the duration of ADT.  

They randomly assigned patients who had received XRT plus 6 months of ADT to two groups, one to receive no further treatment (short-term suppression) and the other to receive 2.5 years of further treatment with ADT (long-term suppression). They found that the 5-year overall mortality for short-term and long-term suppression was 19.0% and 15.2%, respectively ($P > 0.05$). However, prostate-specific survival rates were significantly superior in long-term suppression group ($P = 0.002$).

Denham et al. evaluated short-term ADT (TROG trial) for PCa.  

Their study population consisted of intermediate-risk patients, although the other two study above consisted of high-risk patients. Patients were randomly assigned to receive XRT alone, 3 months of ADT plus XRT, or 6 months of ADT plus XRT. Both ADT groups were starting to androgen suppression 2.5 months before XRT. Six months ADT, decreased distant progression ($P = 0.001$), prostate cancer-specific mortality ($P = 0.0008$), and all-cause mortality ($P = 0.0008$), compared

| Table 3: Radiotherapy alone versus radiotherapy plus ADT series |

| Study (reference) | Year | n | Included patients | Timing of ADT | Median follow-up | Results |
|------------------|------|---|------------------|--------------|-----------------|--------|
| EORTC 22863      | 2010 | 415 | GS 7–10, 33% GS not documented 39% T3 80% PSA >40; 33%, PSA 10–40; 39% | 3 years, immediate pre-XRT Salvage use in XRT only group | 9.1 years | 10 years OS 39.8% versus 58.1% ($P = 0.0001$) 10 years CSS 30.4% versus 10.3% ($P = 0.0001$) |
| RTOG 85-31       | 2005 | 977 | GS 7–10, 70%, LNI 27%, prostatectomy 15% ECE + or LNI+patients Pelvic XRT performed in LNI + patients | Started the last week of XRT and continued indefinitely or until signs of progression | 7.6 years | 10 years OS 39% versus 49% ($P = 0.02$) 10 years CSS 22% versus 12% ($P = 0.001$) |
| RTOG 94-08       | 2011 | 1979 | T1b–T2b, PSA <20 ng ml$^{-1}$ GS 7–10, 36% | XRT with 4 months of ADT starting 2 months before XRT | 9.1 years | 10 years OS 62% versus 57% ($P = 0.03$) 10 years CSS 4% versus 8% ($P = 0.001$) |

OS: overall survival; CSS: cancer-specific mortality; ECE: extracapsular extension; GS: Gleason score; ADT: androgen deprivation therapy; PSA: prostate-specific antigen; XRT: radiotherapy; LNI: lymph node involvement; RTOG: radiation therapy oncology group

| Table 4: The duration of ADT (adjuvant or neo-adjuvant) in combination with radiotherapy |

| Study (reference) | Year | n | ADT duration and timing | Included patients | Median follow-up | Results |
|------------------|------|---|------------------------|------------------|-----------------|--------|
| EORTC-22961      | 2009 | 970 | XRT plus 36 months versus 6 months ADT | LNI + 8%, T3-4 78% GS ≥7, 48%, median age 69 | 6.4 years | 5 years OM 15.2% versus 19% ($P = 0.05$) |
| TROG trial       | 2011 | 802 | 3 or 6 months ADT starting 2–5 months before XRT | T2b-4N0M0, GS 7; 39% GS 8–10; 17%, T3-4 40% PSA ≥20 38% | 10.6 years | 6 months of ADT improved CSS ($P = 0.0008$) and OS ($P = 0.0008$) |
| RTOG 92-02       | 2003 | 1514 | 4 versus 28 months ADT starting 2 months before XRT | T2c-T4 PCa, T3-4 55%, PSA >30; 33%, GS 8–10; 26%, N + 4% | 5.8 years | DFS LT-ADT 46% ST-ADT 28.1% ($P = 0.0001$) |

OM: overall mortality; CSS: cancer-specific mortality; LNI: lymph node involvement; ECE: extracapsular extension; GS: Gleason score; LT-ADT: long-term androgen deprivation therapy; ST-ADT: short-term androgen deprivation therapy; PSA: prostate-specific antigen; XRT: radiotherapy; CSS: cancer-specific survival; OS: overall survival; DFS: disease-free survival; RTOG: radiation therapy oncology group
with XRT alone. In contrast, 3 months ADT had no effect on distant progression, prostate cancer-specific mortality, or all-cause mortality, compared with XRT alone.

EAU prostate cancer guideline recommended long-term ADT before and during XRT for high-risk patients.\(^6\) Additionally, EAU guideline recommended XRT plus long-term ADT in patients with locally advanced PCA (T3–4 N0 M0), who are fit enough to receive XRT; however, the use of ADT alone is recommended inappropriate.\(^6\) NCCN guideline recommended XRT alone in patients with very low-risk group and expected survival over 20 years and in low-risk disease with expected survival over 10 years.\(^3\) They recommended XRT plus 4–6 months ADT in intermediate-risk patients. They also recommended XRT plus 2–3 years ADT in high-risk and very high-risk patients.\(^3\)

POSTPROSTATECTOMY RADIOTHERAPY

Radical prostatectomy for localized prostate cancer provides long-term cancer control.\(^{20}\) In a recent report, a total of 4478 men underwent anatomical radical retropubic prostatectomy without neo-adjuvant or adjuvant therapy with a median follow-up of 10 years. Considerably high overall 25-year progression-free, metastasis-free and cancer-specific survival rates were reported as 68%, 84%, and 86%, respectively.\(^{20}\) On the other hand, it is very well-known that this operation also provides quite reasonable functional outcome. “Trifecta,” meaning, state of being continent, potent and free from cancer has been described for oncological and functional outcome after radical prostatectomy. In this report, actuarial 15 years trifecta was reported as 60%, and progression-free survival (PFS), and cancer-specific survival (CSS) was reported as 60%, 75%, and 89%, respectively. Reportedly, PCA was the reason of death in only 32% of the cases.\(^{20}\)

Although radical prostatectomy provides excellent local control for the organ-confined disease, when the tumor extends beyond the prostatic capsule, the risk of local relapse is increased. After anatomic radical retropubic prostatectomy, in a series of 1623 men, a detectable PSA was reported to be the only evidence of recurrence in 7.9%, while 2.5% recurred locally and 5.4% developed metastases. Actuarial rates at 10 years were 18% for development of an isolated PSA recurrence, 8% for local recurrence, and 9% for distant recurrence.\(^{21}\) In the presence of extra prostatic extension or invasion of the seminal vesicles (pT3), the risk of local failure increases to a level between 10% and 50%.\(^{22,24}\) Connolly et al. in the past and Studer and friends recently showed that local recurrence mostly occur at the vesicourethral anastomosis area followed by the region where vasa deferentia were transected, bladder neck, and posterior to the trigon.\(^{25,26}\) This population of patients may benefit from further local therapy to secure long-term disease control. In turn, they may require adjuvant or salvage radiotherapy for possible definitive treatment.

Immediate postoperative radiotherapy, before waiting for PSA relapse, has been addressed in a number of nonrandomized and randomized studies. Three prospective randomized trials have assessed the role of immediate postoperative XRT in patients with adverse pathological features (i.e., seminal vesicle invasion [SVI], positive surgical margins [PSM] and/or extraprostatic extension [EPE]) and they are summarized in Tables 5 and 6.\(^{27–29}\)

Thompson et al. published the SWOG 8794 trial for evaluating the impact of adjuvant XRT in patients with adverse pathologic findings after radical prostatectomy.\(^{27}\) They randomly assigned patients into 60–64 Gy XRT versus “wait-and-see” groups. The primary outcome was metastases-free survival, defined as time to first evidence of metastatic disease or death due to any cause. Their median follow-up was about 13 years. They showed that adjuvant XRT significantly improved the metastasis-free survival, with a 10-year metastasis-free survival of 71% versus 61% (\(P = 0.016\)) and a 10-year OS of

| Table 5: Randomized clinical trials for adjuvant radiotherapy after radical prostatectomy |
|------------------------------------------|
| Study (references) | n | Patient selection | Randomization | Definition of biochemical recurrence PSA (ng ml\(^{-1}\)) | Median follow-up (months) | bPFS | OS |
| SWOG 8794\(^{27}\) | 431 | pT3 cN0 (involved SM) | 60–64 Gy versus “wait-and-see” | >0.4 | 152 | 10 years: 53% versus 30% (\(P<0.05\)) | 10 years: 74% versus 66% (\(P=0.023\)) |
| ARO 96-02\(^{28}\) | 388 | pT3 (involved SM) pN0, PSA Post-RP undetectable | 60 Gy versus “wait-and-see” | >0.05 plus confirmation | 54 | 5 years: 72% versus 54% (\(P=0.015\)) | Not provided |
| EORTC 22911\(^{29}\) | 1005 | pT3 (involved SM) pN0, pT2 involved SM pN0 | 60 Gy versus “wait-and-see” | >0.4 | 127 | 10 years: 60.6% versus 81% (\(P=0.001\)) | 77% (\(P<0.05\)) |

SM: surgical margin; PSA: prostate-specific antigen; RP: radical prostatectomy; bPFS: biochemical progression-free survival; OS: overall survival

| Table 6: Randomized clinical trials for adjuvant radiotherapy after radical prostatectomy: the outcomes in the subgroup analyses |
|------------------------------------------|
| Study (references) | Positive margins | Extra prostatic extension | Seminal vesicle involvement |
| SWOG 8794\(^{27}\) | bRFS: Observation < XRT (HR=0.44, CI=0.3–0.65) | cRFS: Observation < XRT (HR=0.64, CI=0.45–0.93) | bRFS: Observation < XRT (HR=0.49, CI=0.40–0.60) | cRFS: Observation > XRT (HR=0.83, CI=0.65–1.05) | OS: Observation > XRT (HR=1.16, CI=0.88–1.54) |
| ARO 96-02\(^{28}\) | bRFS: Observation < XRT (HR=0.41, CI=0.25–0.66) | bRFS: Observation < XRT (pT3a/b: HR=0.34, CI=0.19–0.64) | bRFS: Observation < XRT (pT3c: HR=0.77, CI=0.42–1.40) | cRFS: Observation > XRT (HR=0.49, CI=0.40–0.60) | cRFS: Observation > XRT (HR=0.83, CI=0.65–1.05) | OS: Observation > XRT (HR=1.16, CI=0.88–1.54) |
| EORTC 22911\(^{29}\) | bRFS: Observation < XRT (HR=0.44, CI=0.35–0.75) | cRFS: Observation < XRT (HR=0.69, CI=0.53–0.91) | OS: Observation > XRT (HR=0.98, CI=0.72–1.34) | bRFS: Observation < XRT (HR=0.49, CI=0.40–0.60) | cRFS: Observation > XRT (HR=0.83, CI=0.65–1.05) | OS: Observation > XRT (HR=1.16, CI=0.88–1.54) |

bRFS: biochemical recurrence-free survival; cRFS: clinical recurrence-free survival; OS: overall survival; CI: confidence interval; HR: hazard ratio
According to the study, the impact of adjuvant XRT was significant compared to the radical prostatectomy only group. Additionally, Bolla et al. found that immediate postoperative XRT after surgery significantly improved the 10-year biological PFS to 60.6% versus 41.1% in the observation group. OS did not differ significantly between the treatment arms. In the subgroup analyses, they found significant improvement in bRFS and cRFS in patients with +PSM. The study reported OS data for this subgroup; there were no differences in OS between patients who did or did not receive XRT in this subgroup. In patients with SVI, the study reported significantly improved bRFS with XRT, but XRT did not improve clinical RFS. In patients with EPE, the study reported significantly improved bRFS with use of XRT, but no differences in cRFS or OS.

ASCO/AUA guideline showed a meta-analysis of all three trials. The meta-analysis of biochemical recurrence data yielded a pooled hazard ratio of 0.48 (95% confidence interval: 0.42–0.56; \( P = 0.00001 \)). ASCO/AUA guideline recommended that physicians should offer adjuvant XRT to patients with adverse pathologic findings at prostatectomy including +PSM, EPE, and/or SVI because of the demonstrated reductions in biochemical recurrence, local recurrence and clinical progression. Additionally, they recommended that patients should be informed that the effectiveness of XRT for PSA recurrence is greatest when given at lower levels of PSA. Confirmatory subgroup analyses from SWOG 8794 indicated that among patients with detectable PSA at the time of XRT, those with PSA values \( \leq 10 \) ng ml\(^{-1} \) had higher 5- and 10-year bRFS rates than those with pre-XRT PSA values \( >10 \) ng ml\(^{-1} \). In addition, Stephenson et al. evaluated the timing of salvage XRT after radical prostatectomy. They estimated that 48% of the patients who received salvage XRT alone without ADT when PSA was 0.50 ng ml\(^{-1} \) or less were disease-free at 6 years, compared with 40%, 28%, and 18% of those treated when PSA levels were between 0.51 to 1.00, 1.01 to 1.50, and \( >1.50 \) ng ml\(^{-1} \), respectively. Therefore, patients should be advised that XRT should be administered at the earliest sign of PSA recurrence and, ideally, before PSA rises to 1.0 ng ml\(^{-1} \).

EAU Prostate cancer guideline also concluded that for patients classified as pT3 pN0 with a high-risk of local failure after radical prostatectomy due to positive margins (highest impact), capsule rupture, and/or invasion of the seminal vesicles, who present with a PSA level of \( <0.1 \) ng ml\(^{-1} \), two options can be offered in the framework of informed consent. These are; immediate adjuvant XRT to the surgical bed after recovery of urinary function or clinical and biological monitoring followed by salvage radiotherapy (SRT) before the PSA exceeds 0.5 ng ml\(^{-1} \). EAU guideline recommended that in patients with pathological tumor stage T3 N0 M0, immediate postoperative external irradiation after radical prostatectomy may improve the biochemical and clinical disease-free survival, with the highest impact in cases of positive margins.

NCCN guidelines recommended adjuvant/salvage XRT in all men with adverse pathological findings or detectable PSA and no evidence of disseminated disease. Indications for adjuvant XRT include pT3 disease, positive margin(s), Gleason score 8–10, or seminal vesicle involvement. Patients with +PSM and PSA doubling time \( >9 \) months may benefit the most.

**Radiotherapy Toxicity**

The toxicity of XRT is evaluated regarding the toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC).

The toxicity of XRT categorized as genitourinary (GU) or gastrointestinal (GI). EORTC/RTOG acute radiation morbidity scoring criteria; grade 0 (no symptoms), grade 1 (minor symptoms requiring no treatment), grade 2 (symptoms responding to simple outpatient management), grade 3 (distressing symptoms altering XRT, hospitalization for diagnosis or minor surgical intervention may be required), grade 4 (Major surgical intervention or prolonged hospitalization required), grade 5 (Fatal complication).

The risks of mild and more severe GU toxicity in general were 20%–67% and 1%–35%, respectively in different studies. The risks of mild and more severe GI toxicity in general were 2.6%–57% and 1%–26%, respectively in different studies. Up to two-fold, increases in radiation-induced rectal toxicities have been reported in dose-escalated XRT arms compared to lower dose control arms in a number of randomized studies.

Late toxicity was analyzed using a dose of 70 Gy in a prospective EORTC randomized trial 22863 (1987–1995). A total of 377 patients were evaluable for long-term toxicity. 86 patients (22.8%) had grade \( \geq 2 \) urinary or intestinal complications or leg edema, 72 of whom had grade 2 (moderate) toxicity, while 10 had grade 3 (severe) toxicity and 4 died due to grade 4 (fatal) toxicity.
The risk of erectile dysfunction after XRT in general was 7%–63% in different studies. Robinson et al. published a meta-analysis and they found the predicted probability of maintaining erectile function after XRT 0.55, after nerve-sparing radical prostatectomy 0.34, after standard radical prostatectomy 0.25.

The toxicity of postprostatectomy XRT was analyzed in one meta-analysis with the pooled data from the ARO and SWOG trials. It demonstrated a 10% stricture rate with adjuvant XRT compared with 5.8% in the wait-and-see arm at 10 years, which was statistically significant. Incontinence was observed in 6.5% versus 2.8% in the adjuvant XRT versus observation arm, respectively. In the EORTC trial, any grade 3 toxicity was seen in only 4.2% of men in the postoperative XRT arm, compared with 2.6% in the wait-and-see arm. In terms of potency rates, the SWOG trial reported that the proportion of men with ED significantly decreased over time but did not vary significantly according to treatment arm.

There is a risk of second primary malignancy after radiation although patients who have had prostate cancer are most likely to get these lesions in the rectum and bladder. Brenner et al. estimated risk of developing a radiation-associated second malignancy was 1 in 290 for all prostate carcinoma patients treated with XRT, increasing to 1 in 70 for long-term survivors (over 10 years). They found that XRT for prostate carcinoma was associated with a small, statistically significant increase in the risk of solid tumors (6%; P = 0.02) relative to treatment with surgery. Among patients who survived for >5 years, the increased relative risk reached 15%, and was 34% for patients surviving over 10 years. Baxter et al. published a study for the increasing risk of rectal cancer after the irradiation of prostate. They found that radiation was independently associated with the development of cancer over time in irradiated sites (rectum). They found the adjusted hazard ratio for the development of rectal cancer was 1.7 for the radiation group compared with the surgery-only group.

EAU prostate cancer guideline recommended that patients must be informed about the potential for late GU or GI toxicity and the impact of irradiation on erectile function.

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