Asian Journal of Andrology (2015) 17, 892–898

www.asiaandro.com; www.ajandrology.com

Open Access

INVITED RESEARCH HIGHLIGHT

Prostate Cancer

External beam radiotherapy for localized prostate cancer

Hasan Yilmaz[1], Gorkem Aksu[2], Ozdal Dillioglugil[1]

Asian Journal of Andrology (2015) **17**, 892–898; doi: 10.4103/1008-682X.156857; published online: 26 June 2015

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 Network[1] and/or D'Amico prognostic factor classification[2]).

Patient comorbidity can be evaluated with Charlson score.[3,4] 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.[5] 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.[1,6] 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.[6]

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 trail.[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).

[1]Kocaeli University, School of Medicine, Department of Urology, Kocaeli, Turkey; [2]Kocaeli University, School of Medicine, Department of Radiation Oncology, Kocaeli, Turkey.
Correspondence: Dr. O Dillioglugil (odillioglugil@gmail.com)
*This article is based on a presentation delivered on the International Prostate Forum at the Annual Meeting of the American Urological Association, Orlando, Fl, USA, May 18, 2014.

Table 1: Prostate cancer progression risk classification

	Very low-risk	*Low-risk*	*Intermediate-risk*	*High-risk*	*Very high-risk*
D'Amico (AUA)	-	PSA <10 ng ml^{-1}, and GS <7, and cT1–2a	PSA 10–20 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 ng ml^{-1}, GS <7, cT1–2a	PSA 10–20 ng ml^{-1}, or GS=7, or cT2b–2c	PSA >20 ng ml^{-1}, or GS >7, or cT3a	cT3b–4
EAU	-	PSA <10 ng ml^{-1}, GS <7, cT1c	PSA 10–20 ng ml^{-1}, or GS=7, or cT2b–2c	PSA >20 ng ml^{-1}, or GS 8–10, 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[10]	2011	301	Intermediate-risk 70% High-risk 30%	70 versus 78	9 years	CSS High-risk; 86% versus 96% PSA >10; 85% versus 98%
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 RT01[8]	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[7]	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 invovement; GS: gleason score; ADT: androgen deprivation therapy; PSA: prostate-specific antigen; BF: biochemical failure

Dearnaley *et al*. published the MRC-RT01 trial that compared standard 64 Gy versus 74 Gy XRT.[8] All patients had neo-adjuvant 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.[9] 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.[10] 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.[11] They found BF within 5 years were 28% versus 39%, 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 about 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.[12] 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

up to 81.0 Gy provide improved PSA-assessed disease control.[1]

ROLE OF ANDROGEN DEPRIVATION THERAPY

Androgens are important mitogens in prostate cancer in all phases of the disease.[13] The addition of ADT to XRT improves biochemical and survival outcomes in patients with locally advanced disease or with poor risk factors.[14–16] 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.[14] 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.[15] 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.[16] 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[17–19] and they are summarized in **Table 4**. Hanks *et al*. designed a study (RTOG 92-02) to evaluate the impact of long-term ADT.[17] All patients received 4 months ADT (2 months before and 2 months during 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.[18] 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.[19] 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[15]	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 CSM 30.4% versus 10.3% (P<0.0001)
RTOG 85-31[14]	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 CSM 22% versus 12% (P<0.001)
RTOG 94-08[16]	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 CSM 4% versus 8% (P=0.001)

OS: overall survival; CSM: 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[18]	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[19]	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[17]	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; CSM: 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.[1] 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.[1]

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.[21]

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.[22] 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%.[23,24] 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 (month)*	*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 41% (P<0.001)	81% versus 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)	Not reported	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)
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: Observation < XRT (HR=0.60, CI=0.44–0.82) cRFS: Observation=RT (HR=0.82; CI=0.58–1.16) OS: Observation=RT (HR=1.00, CI=0.66–1.52)

bRFS: biochemical recurrence-free survival; cRFS: clinical recurrence-free survival; OS: overall survival; CI: confidence interval; HR: hazard ratio

74% versus 66% ($P = 0.023$). Additionally, in the subgroup analyses, they found significant improvement in biochemical recurrence-free survival (bRFS) and clinical recurrence-free survival (cRFS) among patients with positive surgical margins (+PSM) who received adjuvant XRT. In the seminal vesicle invasion (SVI) subgroup, they found significant improvement in bRFS with adjuvant XRT, but this did not improve cRFS.

Wiegel *et al.* published the ARO 96-02 trial.[28] This is the only trial in which all patients had an undetectable PSA at the time of XRT. They randomly assigned patients into 60 Gy XRT versus "wait-and-see" groups. The primary outcome was biochemical progression-free survival (bPFS). Their median follow-up was about 13 years. The XRT group demonstrated a significant improvement in bPFS of 72% versus 54%, respectively ($P = 0.0015$). This result indicates that adjuvant XRT is effective, even in the setting of an undetectable PSA after radical prostatectomy. In the subgroup analyses, they also found significant improvement in bRFS in patients with +PSM and extraprostatic extension (EPE) who received adjuvant XRT. However, they reported no difference in bRFS with adjuvant XRT in patients with SVI.

Bolla *et al.* published the EORTC 22911 trial.[29] In this trial, eligible patients ($n = 1005$) were 75 years old or younger, previously untreated, adenocarcinoma of the prostate classified as stage cT0–3, N0 M0 by the Union Internationale Contre le Cancer 1983 tumor–node–metastasis (TNM) classification and pathological stage pT2–3 N0, with at least one of the following risk factors: capsular perforation, positive surgical margins, or seminal vesicle invasion. Patients were randomized to receive immediate postoperative (60 Gy) external irradiation ($n = 502$), or to a wait-and-see policy ($n = 503$) with subsequent treatment (irradiation or other) delayed until biochemical or clinical relapse; irradiation was recommended for local relapse (70 Gy). The primary outcome was initially local control but changed in 1995 to clinical progression-free survival (cPFS). cPFS defined as clinical or imaging evidence of recurrence or death but not including biochemical progression. The study demonstrated improved cPFS and this difference was borderline significant ($P = 0.054$) at the 10 years median follow-up point. The ASCO/AUA guideline concluded that the weaker effect in EORTC 22911 may have been the result of the higher rate of nonprostate cancer mortality among the adjuvant XRT group (17.1%) compared to the radical prostatectomy only group (12.3%) or possibly because salvage treatments in the radical prostatectomy only group were initiated at lower PSA levels than in the adjuvant XRT group.[30] 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.[29]

ASCO/AUA guideline showed a meta-analysis of all three trials.[30] 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.[30] 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 ≤1.0 ng ml^{-1} had higher 5- and 10-year bRFS rates than those with pre-XRT PSA values >1.0 ng ml^{-1}.[27] In addition, Stephenson *et al.* evaluated the timing of salvage XRT after radical prostatectomy.[31] 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}.[30]

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.[6]

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.[1]

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).[32] 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).[32]

The risks of mild and more severe GU toxicity in general were 20%–67% and 1%–35%, respectively in different studies.[33] The risks of mild and more severe GI toxicity in general were 2.6%–57% and 1%–26%, respectively in different studies.[33] 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.[8,34,35]

Late toxicity was analyzed using a dose of 70 Gy in a prospective EORTC randomized trial 22863 (1987–1995).[15] A total of 377 patients were evaluable for long-term toxicity, 86 patients (22.8%) had grade >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.[33] 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.[36]

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.[37] 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.[15] 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.[27]

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).[38] 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.[38] Baxter *et al*. published a study for the increasing risk of rectal cancer after the irradiation of prostate.[37] 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.[6]

EDITORIAL COMMENT – (BY DR. JOHN W DAVIS, DEPARTMENT OF UROLOGY, THE UNIVERSITY OF TEXAS, MD ANDERSON CANCER CENTER, HOUSTON, TEXAS, USA)

As reviewed by Chapin in this issue, many of the arguments for surgery are opinions and judgments with varying levels of supporting evidence. The series of publications from the Scandinavian Prostate Cancer Group Trial 4 stand-out as unique comparisons to surgically treated patients versus watchful waiting. By contrast, for patients considering radiation therapy, there are a series of key studies that must be mastered and presented that cover dose, concomitant androgen deprivation therapy, morbidity, and possible role for postsurgery radiotherapy. Many of these points are more formally studied and incorporated into guidelines with higher levels of evidence. The challenges remain as these high-level studies do not compare surgery to radiation, but rather various forms of radiation strategy.

REFERENCES

1 Network NCC. Clinical Practice Guidelines in Oncology: prostate Cancer (Version 2.2014). Jenkintown, Pennsylvania: NCCN; 2014.
2 Boorjian SA, Karnes RJ, Rangel LJ, Bergstralh EJ, Blute ML. Mayo Clinic validation of the D'amico risk group classification for predicting survival following radical prostatectomy. *J Urol* 2008; 179: 1354–60; discussion 1360–1. PubMed PMID: 18289596.
3 Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. *J Clin Epidemiol* 1994; 47: 1245–51. PubMed PMID: 7722560.
4 Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis* 1987; 40: 373–83. PubMed PMID: 3558716.
5 Albertsen PC, Moore DF, Shih W, Lin Y, Li H, *et al*. Impact of comorbidity on survival among men with localized prostate cancer. *J Clin Oncol* 2011; 29: 1335–41. PubMed PMID: 21357791. Pubmed Central PMCID: 3084001.
6 Mottet N, Bastian JB, Bellmunt J, van den Bergh RC, Bolla M, *et al*. Guidelines on Prostate Cancer. 2014th ed. Arnhem, The Netherlands: EAU Guidelines Office; 2014.
7 Peeters ST, Heemsbergen WD, Koper PC, van Putten WL, Slot A, *et al*. Dose-response in radiotherapy for localized prostate cancer: results of the Dutch multicenter randomized phase III trial comparing 68 Gy of radiotherapy with 78 Gy. *J Clin Oncol* 2006; 24: 1990–6. PubMed PMID: 16648499.
8 Dearnaley DP, Sydes MR, Graham JD, Aird EG, Bottomley D, *et al*. Escalated-dose versus standard-dose conformal radiotherapy in prostate cancer: first results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2007; 8: 475–87. PubMed PMID: 17482880.
9 Zietman AL, Bae K, Slater JD, Shipley WU, Efstathiou JA, *et al*. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from proton radiation oncology group/american college of radiology 95-09. *J Clin Oncol* 2010; 28: 1106–11. PubMed PMID: 20124169. Pubmed Central PMCID: 2834463.
10 Kuban DA, Levy LB, Cheung MR, Lee AK, Choi S, *et al*. Long-term failure patterns and survival in a randomized dose-escalation trial for prostate cancer. Who dies of disease? *Int J Radiat Oncol Biol Phys* 2011; 79: 1310–7. PubMed PMID: 20493642.
11 Beckendorf V, Guerif S, Le Prisé E, Cosset JM, Bougnoux A, *et al*. 70 Gy versus 80 Gy in localized prostate cancer: 5-year results of GETUG 06 randomized trial. *Int J Radiat Oncol Biol Phys* 2011; 80: 1056–63. PubMed PMID: 21147514.
12 Zelefsky MJ, Pei X, Chou JF, Schechter M, Kollmeier M, *et al*. Dose escalation for prostate cancer radiotherapy: predictors of long-term biochemical tumor control and distant metastases-free survival outcomes. *Eur Urol* 2011; 60: 1133–9. PubMed PMID: 21889832. Pubmed Central PMCID: 4037155.
13 Khor R, Williams S. Contemporary issues in radiotherapy for clinically localized prostate cancer. *Hematol Oncol Clin North Am* 2013; 27: 1137–62, vii. PubMed PMID: 24188256.
14 Pilepich MV, Winter K, Lawton CA, Krisch RE, Wolkov HB, *et al*. Androgen suppression adjuvant to definitive radiotherapy in prostate carcinoma – long-term results of phase III RTOG 85-31. *Int J Radiat Oncol Biol Phys* 2005; 61: 1285–90. PubMed PMID: 15817329.
15 Bolla M, Van Tienhoven G, Warde P, Dubois JB, Mirimanoff RO, *et al*. External irradiation with or without long-term androgen suppression for prostate cancer with high metastatic risk: 10-year results of an EORTC randomised study. *Lancet Oncol* 2010; 11: 1066–73. PubMed PMID: 20933466.
16 Jones CU, Hunt D, McGowan DG, Amin MB, Chetner MP, *et al*. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med* 2011; 365: 107–18. PubMed PMID: 21751904.
17 Hanks GE, Pajak TF, Porter A, Grignon D, Brereton H, *et al*. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol* 2003; 21: 3972–8. PubMed PMID: 14581419.
18 Bolla M, de Reijke TM, Van Tienhoven G, Van den Bergh AC, Oddens J, *et al*. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med* 2009; 360: 2516–27. PubMed PMID: 19516032.
19 Denham JW, Steigler A, Lamb DS, Joseph D, Turner S, *et al*. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. *Lancet Oncol* 2011; 12: 451–9. PubMed PMID: 21440505.
20 Mullins JK, Feng Z, Trock BJ, Epstein JI, Walsh PC, *et al*. The impact of anatomical radical retropubic prostatectomy on cancer control: the 30-year anniversary. *J Urol* 2012; 188: 2219–24. PubMed PMID: 23083655.
21 Bianco FJ Jr, Scardino PT, Eastham JA. Radical prostatectomy: long-term cancer control and recovery of sexual and urinary function ("trifecta"). *Urology* 2005; 66 5 Suppl: 83–94. PubMed PMID: 16194712.
22 Pound CR, Partin AW, Epstein JI, Walsh PC. Prostate-specific antigen after anatomic radical retropubic prostatectomy. Patterns of recurrence and cancer control. *Urol Clin North Am* 1997; 24: 395–406. PubMed PMID: 9126237.
23 Epstein JI, Carmichael M, Partin AW, Walsh PC. Is tumor volume an independent predictor of progression following radical prostatectomy? A multivariate analysis of 185 clinical stage B adenocarcinomas of the prostate with 5 years of followup. *J Urol* 1993; 149: 1478–81. PubMed PMID: 8501792.
24 Myers RP, Fleming TR. Course of localized adenocarcinoma of the prostate treated by radical prostatectomy. *Prostate* 1983; 4: 461–72. PubMed PMID: 6889191.
25 Connolly JA, Shinohara K, Presti JC Jr, Carroll PR. Local recurrence after radical prostatectomy: characteristics in size, location, and relationship to prostate-specific antigen and surgical margins. *Urology* 1996; 47: 225–31. PubMed PMID: 8607239.

26 Nguyen DP, Giannarini G, Seiler R, Schiller R, Thoeny HC, *et al*. Local recurrence after retropubic radical prostatectomy for prostate cancer does not exclusively occur at the anastomotic site. *BJU Int* 2013; 112: E243–9. PubMed PMID: 23186331.

27 Thompson IM, Tangen CM, Paradelo J, Lucia MS, Miller G, *et al*. Adjuvant radiotherapy for pathological T3N0M0 prostate cancer significantly reduces risk of metastases and improves survival: long-term followup of a randomized clinical trial. *J Urol* 2009; 181: 956–62. Pubmed Central PMCID: 3510761.

28 Wiegel T, Bottke D, Steiner U, Siegmann A, Golz R, *et al*. Phase III postoperative adjuvant radiotherapy after radical prostatectomy compared with radical prostatectomy alone in pT3 prostate cancer with postoperative undetectable prostate-specific antigen: ARO 96-02/AUO AP 09/95. *J Clin Oncol* 2009; 27: 2924–30. PubMed PMID: 19433689.

29 Bolla M, van Poppel H, Tombal B, Vekemans K, Da Pozzo L, *et al*. Postoperative radiotherapy after radical prostatectomy for high-risk prostate cancer: long-term results of a randomised controlled trial (EORTC trial 22911). *Lancet* 2012; 380: 2018–27. PubMed PMID: 23084481.

30 Thompson IM, Valicenti RK, Albertsen P, Davis BJ, Goldenberg SL, *et al*. Adjuvant and salvage radiotherapy after prostatectomy: AUA/ASTRO Guideline. *J Urol* 2013; 190: 441–9. PubMed PMID: 23707439.

31 Stephenson AJ, Scardino PT, Kattan MW, Pisansky TM, Slawin KM, *et al*. Predicting the outcome of salvage radiation therapy for recurrent prostate cancer after radical prostatectomy. *J Clin Oncol* 2007; 25: 2035–41. PubMed PMID: 17513807. Pubmed Central PMCID: 2670394.

32 Cox JD, Stetz J, Pajak TF. Toxicity criteria of the Radiation Therapy Oncology Group (RTOG) and the European Organization for Research and Treatment of Cancer (EORTC). *Int J Radiat Oncol Biol Phys* 1995; 31: 1341–6. PubMed PMID: 7713792.

33 Bhatnagar V, Stewart ST, Huynh V, Jorgensen G, Kaplan RM. Estimating the risk of long-term erectile, urinary and bowel symptoms resulting from prostate cancer treatment. *Prostate Cancer Prostatic Dis* 2006; 9: 136–46. PubMed PMID: 16402091.

34 Al-Mamgani A, van Putten WL, Heemsbergen WD, van Leenders GJ, Slot A, *et al*. Update of Dutch multicenter dose-escalation trial of radiotherapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2008; 72: 980–8. PubMed PMID: 18495377.

35 Zietman AL, DeSilvio ML, Slater JD, Rossi CJ Jr, Miller DW, *et al*. Comparison of conventional-dose vs high-dose conformal radiation therapy in clinically localized adenocarcinoma of the prostate: a randomized controlled trial. *JAMA* 2005; 294: 1233–9. PubMed PMID: 16160131.

36 Robinson JW, Moritz S, Fung T. Meta-analysis of rates of erectile function after treatment of localized prostate carcinoma. *Int J Radiat Oncol Biol Phys* 2002; 54: 1063–8. PubMed PMID: 12419432.

37 Baxter NN, Tepper JE, Durham SB, Rothenberger DA, Virnig BA. Increased risk of rectal cancer after prostate radiation: a population-based study. *Gastroenterology* 2005; 128: 819–24. PubMed PMID: 15825064.

38 Brenner DJ, Curtis RE, Hall EJ, Ron E. Second malignancies in prostate carcinoma patients after radiotherapy compared with surgery. *Cancer* 2000; 88: 398–406. PubMed PMID: 10640974.