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Task Group/Practice Parameter

American Brachytherapy Society Task Group Report: Combination of brachytherapy and external beam radiation for high-risk prostate cancer

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ABSTRACT

PURPOSE: To review outcomes for high-risk prostate cancer treated with combined modality radiation therapy (CMRT) utilizing external beam radiation therapy (EBRT) with a brachytherapy boost.

METHODS AND MATERIALS: The available literature for high-risk prostate cancer treated with combined modality radiation therapy was reviewed and summarized.

RESULTS: At this time, the literature suggests that the majority of high-risk cancers are curable with multimodal treatment. Several large retrospective studies and three prospective randomized trials comparing CMRT to dose-escalated EBRT have demonstrated superior biochemical control with CMRT. Longer followup of the randomized trials will be required to determine if this will translate to a benefit in metastasis-free survival, disease-specific survival, and overall survival. Although greater toxicity has been associated with CMRT compared to EBRT, recent studies suggest that technological advances that allow better definition and sparing of critical adjacent structures as well as increasing experience with brachytherapy have improved implant quality and the toxicity profile of brachytherapy. The role of androgen deprivation therapy is well established in the external beam literature for high-risk disease, but there is controversy regarding the applicability of these data in the setting of dose escalation. At this time, there is not sufficient evidence for the omission of androgen deprivation therapy with dose escalation in this population. Comparisons with surgery remain limited by differences in patient selection, but the evidence would suggest better disease control with CMRT compared to surgery alone.

CONCLUSIONS: Due to a series of technological advances, modern combination series have demonstrated unparalleled rates of disease control in the high-risk population. Given the evidence from recent randomized trials, combination therapy may become the standard of care for high-risk cancers. © 2016 American Brachytherapy Society. Published by Elsevier Inc. All rights reserved.

Keywords: Prostate cancer therapy; Combination brachytherapy and external beam radiation; High-risk prostate cancer

Introduction

Approximately 225,000 men are diagnosed with prostate cancer in the United States each year, while only 30,000 die from the disease (1). Furthermore, most men die with prostate cancer rather than from the disease (2). These statistics demonstrate that prostate cancer is a heterogeneous disease that can often present as a chronic indolent process, but in a subset of men, it can be a highly

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aggressive life-threatening disease. Multiple risk stratification schemas for prostate cancer have been proposed based on various clinicopathologic features including Gleason Score (GS), TNM stage, and baseline prostate-specific antigen (PSA) in an attempt to define distinct prognostic groups of patients to facilitate clinical decision making and research investigation (3–6). The National Comprehensive Cancer Network is one of the most widely used risk classification systems used in the United States and presently divides patients into five risk groups: very low, low, intermediate, high, and very high (3), Based on current clinical practices, the rates of failing definitive therapy are markedly different across risk groups and range from <1% for very low-risk patients to >70% for very high-risk men (7, 8). Furthermore, although the risk of death from prostate cancer is less than 5% for men with very low, low, or select intermediate-risk prostate cancer, greater than 15% of men with high and very high-risk prostate cancer succumb to their disease (7).

Primarily due to the introduction of PSA screening in the early 1990s, there has been a significant downward stage migration for men with prostate cancer. For instance, in 1989, >40% of men diagnosed with prostate cancer were classified as high risk. This is in contrast to 2002 where only 15% of men are classified as high risk (9). However, this stage migration has clearly identified a more biologically aggressive disease that warrants multimodality therapy. There are currently multiple different treatment methods employed in high-risk prostate cancer including surgery alone, external beam radiation therapy (EBRT) with androgen deprivation therapy (ADT), and a combination of external beam radiation, brachytherapy, and ADT. Given that a high number of patients in this category fail treatment and even die of their disease, it is necessary to further improve the treatment strategy for high and very high-risk prostate cancer patients.

Progress in the management of high-risk disease has come from a multifaceted approach, including early diagnosis to identify such cancers at a curable point, imaging for detection of aggressive lesions (10, 11), subclassification of the most lethal forms of high-risk prostate cancer (12–14), improved surgical and radiation techniques (15), earlier introduction of chemotherapy (16), and multidisciplinary coordination of care. Yet perhaps the greatest progress has come from a major conceptual change in treating men with high-risk prostate cancer. High-risk prostate cancer was generally regarded as a disease that by definition harbored micrometastatic disease. This concept drove the search for systemic agents, primarily agents that inhibited androgen receptor signaling, in hopes of treating micrometastatic disease.

ADT by means of surgical or chemical castration has been the most commonly studied form of therapy to treat metastatic disease. It is clear from randomized trials that the addition of ADT to radiotherapy improves outcomes over radiotherapy alone and that the addition of radiotherapy to ADT improves outcomes over ADT alone (17, 18). However, it is unclear if the use of ADT primarily acts to reduce micrometastatic disease or principally to provide radiosensitization to improve local control. It has been demonstrated that ADT inhibits DNA repair and improves the efficacy of radiotherapy *in vitro* by providing a biologically driven form of dose escalation (19, 20). Furthermore, postradiotherapy biopsies from RTOG 9408, a phase III randomized clinical trial comparing radiotherapy to radiotherapy combined with ADT, demonstrated that there was a 50% reduction in biopsy-detected persistent disease locally within the prostate with the addition of ADT (17). This dramatic improvement in local control appeared to translate in a reduction in distant metastases and death from prostate cancer. The incorporation of MRI in prostate cancer staging and treatment planning has allowed

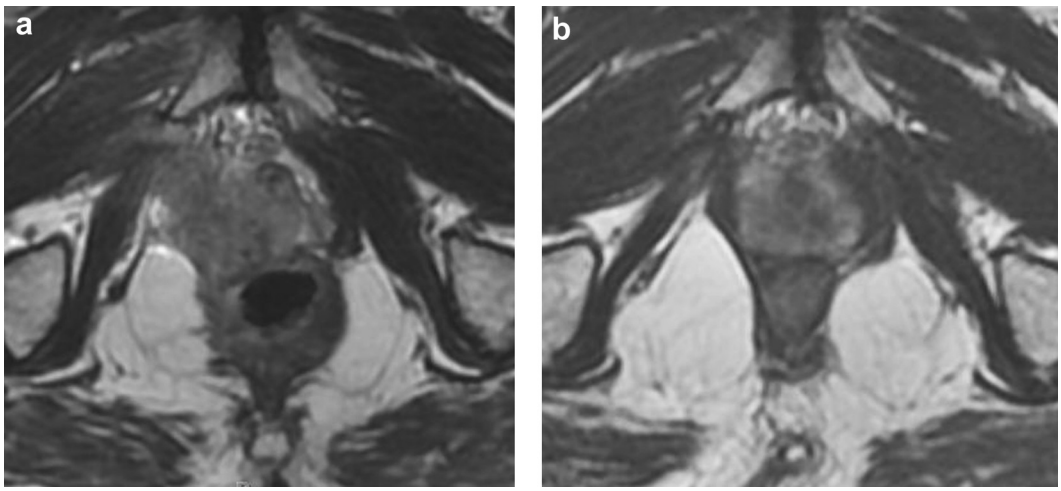

Fig. 1. T2 weighted axial MRI images at the level of the prostate apex demonstrating local effect of ADT. (a) Image taken prior to ADT. (b) Image taken post ADT.

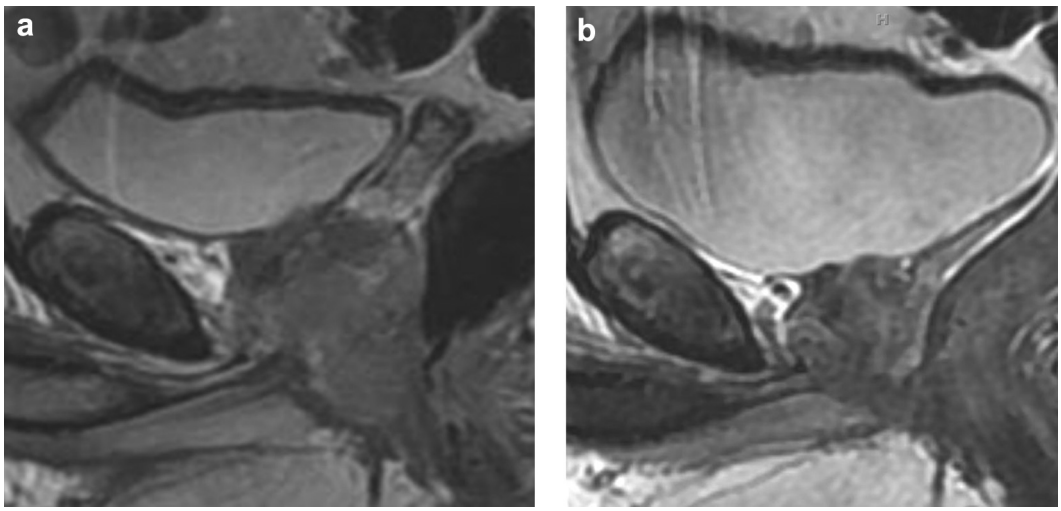

Fig. 2. T2 weighted sagittal MRI images demonstrating local effect of ADT. (a) Image taken prior to ADT demonstrating tumor extension below the penile bulb. (b) Image taken post-ADT demonstrating shrinkage of disease.

radiographic visualization of the impact of ADT on locally advanced disease (Figs. 1–3) (21, 22). These tumor responses further suggest a large proportion of the effect of ADT combined with EBRT is local tumor response. Similarly, men with aggressive local disease who undergo radical prostatectomy followed by further local therapy with adjuvant radiotherapy seem to derive a benefit in progression-free survival, freedom from metastasis, disease-specific survival, and overall survival when local control is established (23). Thus, it is clear that improving local control of prostate cancer translates into improved disease-specific and overall survival in men with high-risk disease. This concept has led many investigators to identify other ways to intensify local therapy with the use of ultra–high-dose escalation to achieve high rates of local control using a combination of external beam radiotherapy and a brachytherapy boost.

In this review, we will summarize recent progress in combined external beam and brachytherapy approaches for high-risk prostate cancer as a powerful form of dose escalation, and the promising long-term outcomes suggesting that CMRT may be the optimal treatment for high-risk prostate cancer.

Data review

This American Brachytherapy Society task group is a collaboration of brachytherapists that was formulated to review and report the technological and clinical evolution of combined modality radiation therapy. We searched PubMed using combinations of the terms: Prostate, High-risk, Brachytherapy, Implant, High-dose-rate, Low-dose-rate, and prostatectomy. In reviewing the development of modern techniques

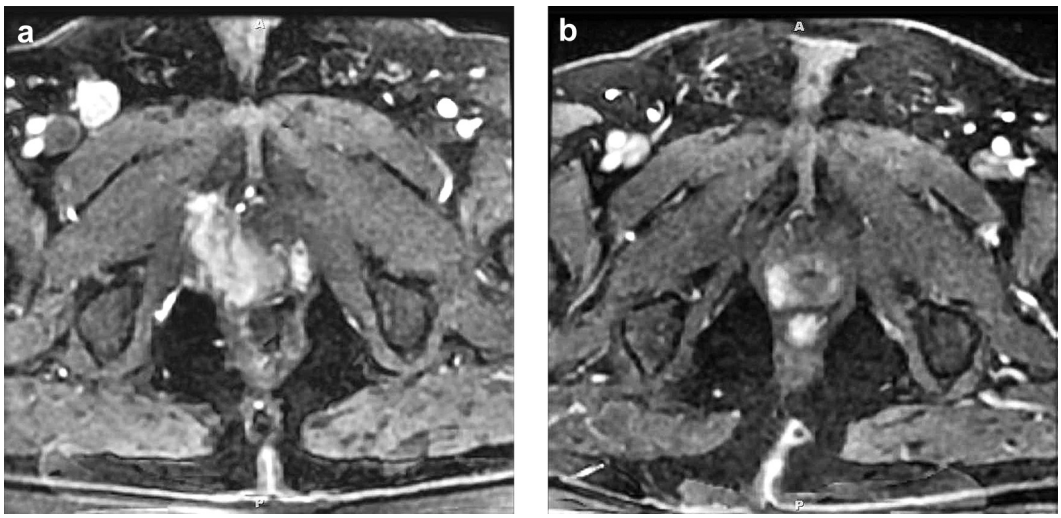

Fig. 3. Dynamic contrast enhanced (DCE) axial MRI images depicting disease infiltrating pelvic muscles prior to ADT (a) and resolution post-ADT (b).

and in reviewing toxicity from CMRT, all applicable manuscripts were reviewed. In evaluating clinical outcomes, manuscripts were restricted to those that reported at least 8-year followup on clinical high-risk patients. High-quality data such as that from prospective randomized controlled trials with shorter followup were included. Manuscripts that did not separate the outcomes for high-risk patients from patients with more favorable disease were excluded. Surgical series that reported outcomes based on pathologic stage and GS as opposed to clinical stage and GS were excluded.

Technical foundation for modern combination therapy

In the late 1980s, ultrasound-guided transperineal brachytherapy replaced open retropubic implant techniques for the insertion of low-dose-rate (LDR) Iodine 125 (^{125}I) seeds. Open implants were pioneered at Memorial Sloan Kettering in the 1970s, but were abandoned primarily because of technical failures. Critz continued open seed implantation, but consistently followed this with external beam radiation therapy (EBRT), making the argument that despite imperfect technique, seed implant provides a tremendous advantage by dose escalation. Critz also insisted on using a very stringent end point of PSA $<$ 0.2 ng/mL, an approach that consistently overestimates clinically significant failure in the short term. However, this allowed direct and competitive comparison with surgical outcomes. When 10-year outcomes were reported in 2004, high-risk patients had a 60% biochemical control rate by this standard. This was a substantial improvement over the best EBRT results of that era, despite the fact that neoadjuvant hormone therapy was not employed (24). A second large report of CMRT from this early era was the 15-year followup data by Blasko *et al.* These results employed a less stringent failure definition of two rises in PSA, yet high-risk results at 15-year followup were in the range of 68% (25). These results were among the most promising radiation reports for high-risk patients at the time and continue to compare favorably to surgical outcomes today.

A major advance in combination therapy was the improvement in imaging and postimplant dosimetry. Early techniques assumed a stable base position, and depth from the grid was used as a surrogate for base depth during needle placement. This resulted in consistent underdosing of the base and inadvertent dose delivery to the genitourinary (GU) diaphragm below the apex. Two-plane ultrasound revolutionized transperineal therapy and allowed direct depth check on sagittal view for all needles. More recently, the adoption of MRI further improved treatment planning and dose delivery. MRI demonstrated profound variation in individual anatomy, discrediting rules of thumb previously employed to define the prostate in relation to adjacent structures. For example, for many years, the penile bulb had been used as a proxy for the prostate apex, given that it is visible on CT. However, MRI has shown that the prostate apex may be 0.5–3.3 cm from the penile bulb. Employing the 1.5-cm rule (apex is 1.5 cm above the penile bulb) resulted in gross underestimation in some and gross overestimation in others (26). MRI also defined critical erectile tissues thought to be responsible for postradiation erectile dysfunction (ED).

Beginning with the pivotal work by Stock (27) and followed by others, a direct tie between brachytherapy quality and outcomes was established (28). Critical in evaluating implant quality was the ability to compare biologically effective doses of brachytherapy with EBRT. Stock *et al.* proposed one of the first models that allowed a meaningful dose response to be assessed in CMRT patients. The biologically effective dose literature has established guideline dose targets in combined implant therapy to achieve optimal cure rates, similar to the earlier D_{90} targets predicting success in monotherapy (29–33). Two schools of thought emerged from this literature. Some have proposed that combination therapy is advantageous for all patients, including those with low-risk disease, to provide further dose escalation. Others have proposed that with optimal implant quality, brachytherapy as monotherapy could be effective in low- and select intermediate-risk patients. There was consensus that high-risk patients require supplemental EBRT to address disease beyond the prostate, including seminal vesicles and potentially pelvic nodal radiation. At this time, it is unclear who benefits from the addition of pelvic nodal irradiation. This question is being addressed in ongoing clinical trials. RTOG 0924 is currently studying the role of pelvic nodal irradiation in high-risk patients in the setting of dose-escalated radiation therapy and ADT and will be valuable in this realm.

A parallel approach to combined modality treatment with EBRT and permanent seed LDR implant was a vast experience with EBRT combined with high-dose-rate (HDR) brachytherapy. A consistent argument in favor of HDR has been improved dose delivery relative to permanent seed implants and improved coverage of seminal vesicle extension commonly encountered in high-risk patients. Radiobiological studies have suggested that prostate cancer may have a low alpha/beta ratio, which would further support the use of high doses per fraction that are feasible with HDR brachytherapy (34). Historically, HDR combination has been associated with a high risk of stricture formation due to high dose per fraction delivered to the urethra and external sphincter (35). However, this was likely due to technical factors including inadequate imaging and catheter displacement between the first and subsequent fractions, suggesting that such complications could potentially be avoided with proper technique. With improving intraoperative imaging techniques allowing for either ultrasound or MRI guidance during implantation, these technical factors are becoming less of a concern (36, 37). Modern series have reported rates of Grade 3

GU toxicity and urinary strictures that are comparable to other modalities (38, 39). Furthermore, there has been a trend toward using fewer, higher dose fractions of HDR brachytherapy for intermediate- and high-risk patients when performed in combination with EBRT, which reduces the risk of dosimetric variability between fractions. Several series have reported the use of two fractions of 8–10 Gy each and have demonstrated 60–90% biochemical control at 5 years in high-risk patients (40–43). However, few studies have reported 10- to 15-year outcomes and long-term data are limited (44). The challenge with evaluating long-term outcomes with HDR combination series is the significant variability in the delivered dose per fraction and total number of fractions used in the published literature over time and across institutions. This is in stark contrast to LDR brachytherapy, where the dose has been relatively constant over decades. These differences in practice patterns have made it difficult to compare the efficacy of HDR and LDR in the setting of high-risk disease with combination therapy. Nonetheless, recent series from institutions with an exceptional commitment to quality suggest high cure rates can be accomplished with excellent quality of life preservation with either treatment approach (40, 45–47). The American Brachytherapy Society has published guidelines with detailed recommendations regarding dose and treatment parameters for both LDR- and HDR-based combination therapy (48, 49).

Combined modality therapy clinical results

Retrospective data

The first reports of excellent disease control in high-risk patients came from a large retrospective series by Merrick (50, 51). A strategy of wide margins and a high-dose implant assured full dose to the prostate. This resulted in success rates up to 88% for high-risk patients with long followup, a success rate comparable to low/intermediate-risk prostate cancer outcomes. Also reported were toxicities such as prolonged dysuria, later determined to be due to inadvertent dose below the prostate (GU diaphragm region). Merrick also demonstrated that critical prognostic factors that have been identified for failure from EBRT alone (T3, >50% positive biopsy, and Gleason pattern 5) did not predict for failure in high-dose external beam plus brachytherapy combination therapy (52, 53). More recently, Bittner *et al.* (54) reported the outcomes of 406 National Comprehensive Cancer Network high-risk patients treated primarily with combination therapy. The patients were stratified into a good prognostic category based on having only one high-risk feature (GS 8–10, PSA > 20, or cT3) and a poor prognostic category based on having a GS 8–10 and one additional risk factor. This stratification was based on an earlier surgical series by Joniau *et al.* that reported a significant difference in prostate cancer–specific survival among these two prognostic groups when the primary treatment was surgery (95% for good prognostic patients vs. 80% for poor prognostic patients, $p = 0.0003$) (55). However, in Bittner's report, with combination therapy, there were no differences in cause-specific survival. Cause-specific survival reached approximately 95% even in the poor prognostic group. These results suggest that with ultra–high-dose escalation, the recurrence rates even for higher risk disease are so low that routine prognostic factors no longer have a significant impact on outcomes in modest sample sizes. Essentially these wide margin studies overcame the dose delivery questions of other series and suggested a large proportion of men with high-risk disease were curable more often than previously realized with sufficient intensive local therapy.

Confirming these results was a combined institution retrospective review of greater than 900 high-risk patients. In this series, Shilkrut *et al.* (56) compared dose-escalated EBRT and ADT results to EBRT plus brachytherapy with ADT and demonstrated a 27% absolute benefit at 8 years followup in terms of biochemical recurrence-free survival (bRFS) with the addition of a brachytherapy boost (87% vs. 60%, $p < 0.0001$). CMRT was also associated with a prostate cancer–specific mortality benefit of 7% (7% vs. 14%, $p = 0.003$). In a pivotal single institution study, Liss *et al.* (57) reported the benefit of combination therapy for patients with Gleason pattern 5 disease, across all outcomes. Gleason pattern 5 has been well documented as one of the strongest prognostic factors for recurrence and metastases after definitive therapy (12, 13, 58). This report demonstrated that with CMRT, there was a substantial benefit in bRFS (89% vs. 65%, $p < 0.05$), freedom from metastases (89% vs. 67%, $p < 0.05$), cancer-specific survival (93% vs. 78%, $p < 0.05$), and overall survival (88% vs. 67%, $p < 0.05$) at just 5 years after treatment (57). Although the overall survival benefit is likely influenced by selection bias in this retrospective study, it is also likely in part, due to the marked benefit in cancer-specific survival. These data show that in high-risk prostate cancer, achieving local control is paramount in achieving long-term disease-free survival. The long-term retrospective high-risk bRFS results of LDR-based CMRT, HDR-based CMRT, external beam alone, and surgery are included in Table 1.

Prospective clinical trial data

The critical question posed by the retrospective studies was whether patient selection accounted for the superior results seen with combination. Three randomized trials have tested whether dose escalation in the form of combination EBRT and a brachytherapy boost improves outcomes over EBRT alone. All three trials have demonstrated improvements in bRFS with the addition of brachytherapy that spans all risk groups of patients (40, 59, 83). The largest and most recently reported trial, ASCENDE-RT, is a prospective randomized trial that accrued 398 patients with

Table 1
Long-term rates of biochemical recurrence-free survival (bRFS) in clinically high-risk patients

Author	Year	*N*	Treatment	% ADT use	bRFS (%)					bRFS definition
					8 yr	9 yr	10 yr	12 yr	16 yr	
Keyes M (59)	2015	139	LDR + EBRT + ADT	100		78				<PSA Nadir + 2
Marshall *et al.* (60)	2014	421	LDR + EBRT + ADT	100				64		<PSA Nadir + 2
Taira *et al.* (53)	2013	329	LDR + EBRT + ADT	73			91			PSA ≤ 0.4
Shilkrut *et al.* (56)	2013	448	LDR + EBRT + ADT	76	87					<PSA Nadir + 2
Fang *et al.* (51)	2011	113	LDR + EBRT + ADT	100			93			PSA ≤ 0.4
Stock *et al.* (58)	2009	181	LDR + EBRT + ADT	100	73					<PSA Nadir + 2
Merrick *et al.* (61)	2011	284	LDR + EBRT ± ADT	63				89		PSA ≤ 0.4
Taira *et al.* (62)	2011	473	LDR + EBRT ± ADT	58				91		PSA ≤ 0.4
Dattoli *et al.* (63)	2010	164	LDR + EBRT ± ADT	Unknown					74	PSA < 0.2 and <PSA nadir + 2
Bittner *et al.* (64)	2008	243	LDR + EBRT ± ADT	60			89			PSA ≤ 0.4
Johnson *et al.* (65)	2015	115	HDR + EBRT + ADT	95			73			<PSA Nadir + 2
Galalae *et al.* (44)	2014	55	HDR + EBRT + ADT	Unknown			69			<PSA Nadir + 2
Prada *et al.* (46)	2012	294	HDR + EBRT + ADT	Unknown			84			<PSA Nadir + 2
Savdie *et al.* (66)	2012	90	HDR + EBRT + ADT	100			54			<PSA Nadir + 2
Krauss *et al.* (67)	2011	96	HDR + EBRT + ADT	100	58					<PSA Nadir + 2
Martinez *et al.* (68)	2016	485	HDR + EBRT ± ADT	70			54			<PSA Nadir + 2
Krauss *et al.* (67)	2011	60	HDR + EBRT	0	58					<PSA Nadir + 2
Demanes *et al.* (45)	2005	47	HDR + EBRT	Unknown			69			<PSA Nadir + 2
Keyes M (59)	2015	137	EBRT + ADT	100		58				<PSA Nadir + 2
Dearnaley *et al.* (69)	2014	422	EBRT + ADT	100			55			PSA < 1.5 × nadir and <2 ng/mL
Shilkrut *et al.* (56)	2013	510	EBRT + ADT	85	60					<PSA Nadir + 2
Stenmark *et al.* (70)	2011	185	EBRT + ADT	100	69					<PSA Nadir + 2
Zelefsky *et al.* (71)	2008	296	EBRT ± ADT	64			37			<PSA Nadir + 2
Stenmark *et al.* (70)	2011	49	EBRT	0	61					<PSA Nadir + 2
Kuban *et al.* (72)	2008	53	EBRT	0	63					<PSA Nadir + 2
Wiegel *et al.* (73)	2014	148	Surgery + adjuvant RT	11			56			PSA ≤ 0.2
Bolla *et al.* (74)	2012	502	Surgery + adjuvant RT	10			61			PSA ≤ 0.2
Swanson *et al.* (75)	2007	122	Surgery + adjuvant RT	9			58			PSA ≤ 0.4
Wiegel *et al.* (73)	2014	159	Surgery	12			35			PSA ≤ 0.2
Bolla *et al.* (74)	2012	503	Surgery	10			41			PSA ≤ 0.2
Swanson *et al.* (75)	2007	122	Surgery	8			28			PSA ≤ 0.4
Abdollah *et al.* (76)	2015	1100	Surgery	1			50			PSA ≤ 0.2
Joniau *et al.* (55)	2014	1360	Surgery	43			55			PSA ≤ 0.2
Briganti *et al.* (77)	2012	1366	Surgery	30			54			PSA ≤ 0.2
Yamamoto *et al.* (78)	2012	378	Surgery	0			49			PSA ≤ 0.2
Loeb *et al.* (79)	2010	175	Surgery	0			68			PSA ≤ 0.2
Inman *et al.* (80)	2008	236	Surgery	59			39			PSA ≤ 0.2
Bastian *et al.* (81)	2006	220	Surgery	0			27			PSA ≤ 0.2
Ward *et al.* (82)	2005	841	Surgery	51			43			PSA ≤ 0.2

ADT = androgen deprivation therapy; LDR = low dose rate; EBRT = external beam radiation therapy; PSA = prostate-specific antigen; HDR = high dose rate; RT = radiation therapy.

both high-risk and unfavorable intermediate-risk prostate cancer. Patients were randomized to receive either dose-escalated EBRT to 78 Gy or a combination of EBRT to 46 Gy followed by an ^{125}I LDR boost. All of the patients received 1 year of ADT. This trial differs from the two earlier randomized trials in that the earlier trials enrolled fewer patients, included patients with more favorable disease, employed variable use of ADT, and used lower radiation doses than what is accepted in the contemporary age. Approximately 70% of the patients on ASCENDE-RT had high-risk disease ($n = 276$). Early results of this trial with a median followup of 6.5 years have been reported and show a striking benefit in bRFS with combination therapy. Given some controversy of the optimal definition of bRFS, this parameter has been reported both in terms of the surgical definition (PSA < 0.2) allowing appropriate comparison with surgical series and in terms of the Phoenix definition (PSA < nadir +2) allowing comparison with other radiation series. By the surgical definition of bRFS, there was an absolute difference of 51% at 9 years between the LDR-combination arm and the EBRT-alone arm (82.2% vs. 31.5%, $p < 0.0001$) (84). In the 276 high-risk patients, the absolute benefit of an LDR boost for bRFS at 9 years by the Phoenix definition was 20% (78% vs. 58%, $p = 0.05$) (59). A summary of the three randomized trials comparing combination therapy to EBRT can be found in Table 2.

It is important to note that the duration of ADT in both the prospective and retrospective series discussed typically

Table 2
Phase III clinical trials of EBRT vs. EBRT plus brachytherapy

Authors	Year	*N*	Median followup	Risk groups	Outcomes		
					EBRT	Combo	Significance
Sathya *et al.* (83)	2005	104	8.2 years	Low: 0% Intermediate: 40% High: 60%	5 yr bRFS: 39% Post-tx biopsy positive: 51%	71% 24%	SS SS
Hoskin *et al.* (40)	2012	218	7.1 years	Low: 5% Intermediate: 42% High: 53%	7-yr bRFS 48%	66%	SS
ASCENDE-RT (59)	2015	398	6.5 years	Low: 0% Intermediate: 31% High: 69%	9-yr bRFS 58%	78%	SS

EBRT = external beam radiation therapy; bRFS = biochemical recurrence-free survival; SS = statistically significant.

ranges less than the 2–3 years that is recommended with external beam radiation. The value of ADT has been reviewed retrospectively and has often not shown a benefit in the setting of a brachytherapy boost (85). However, retrospective comparisons are subject to selection bias, as often men at highest risk of progression are given ADT. At this time, it is difficult to define a subpopulation of high-risk patients in which ADT can be routinely omitted and it remains a component of standard of care. Additional studies are required to determine the optimal duration of ADT with CMRT, and we would recommend a minimum of 1 year based on the results from ASCEND-RT.

Although biochemical recurrence has typically been viewed as a poor surrogate for overall survival for prostate cancer patients as a whole, in high and very high-risk patients, biochemical recurrence is closely linked to the need for salvage therapies which can greatly impact quality of life in the short term and progress to lethal disease in a significant proportion of failures. The impact of primary treatment on overall survival is often disguised by the use of salvage ADT as there can be a long duration of response to salvage ADT, with a median time to castration-resistant disease of 7 years after radiotherapy. However, salvage ADT and other systemic therapies have significant side effects. Therefore, patients must be fully informed of their risk of recurrence and their likelihood of needing future treatment and their associated side effects and potential impact on quality of life. In the era of shared decision making, all patients should have an informed discussion of the benefits of combination therapy approaches.

Combined modality toxicity

The goal of treatment is both cure and quality of life preservation, including urinary function and sexual quality of life. Perhaps the strongest criticism of ASCENDE-RT is the high rate of late Grade 3 GU toxicity including urinary strictures with brachytherapy. Cumulative incidence of late Grade 3 GU toxicity in the brachytherapy arm was 18.4% compared to 5.2% in the external beam arm ($p < 0.0001$). Half of these complications were urethral strictures. However, there is little correlation between urethral stricture and dose to the prostate in their cohort. Instead, the ASCENDE-RT trialists acknowledge that there were flaws in their implantation technique, including overestimation of the apex and PTV margin further extending into the GU diaphragm, which is the more likely explanation for their toxicity (59, 84). Many of these complications did subside over time and the prevalence of Grade 3 GU toxicity at 5 years reduced to 8.6% in the brachytherapy arm compared to 2.2% in the EBRT-alone arm. In a separate series from the British Columbia Cancer Agency, Chan *et al.* demonstrated that brachytherapy-associated toxicity decreases with increasing experience. In a cohort of 2011 patients who underwent LDR brachytherapy, the rate of RTOG Grade 3 urinary toxicity dropped from 16.8% in the first 500 patients to 2.8% in the last 500 patients (86). These results reinforce that toxicity rates can be reduced over time as centers gain experience to optimize patient selection, implant technique, and treatment planning.

Stock *et al.* published one of the largest series of prostate cancer patients undergoing brachytherapy with 2495 patients, 943 of which received external beam radiation as well. In their experience, although approximately 56% of the cohort had worsening GU symptoms immediately post-implant, the average increase in IPSS from baseline is only approximately 1.9 points after 12 years of followup. Only 10% of their study population had experienced any degree or duration of urinary retention, and the majority of these were acute and short term. There was an association between pretreatment IPSS and urinary retention (60). These investigators have also reported long-term toxicity data on a unique group of men younger than age 60 years who were treated with LDR brachytherapy with or without external beam. In this cohort of 131 patients, Grade 3 GU toxicity occurred in only 4 (3%) patients at a median followup of 11.5 years, all of which were from urinary retention. No significant differences were found between patients who had an implant alone vs. an implant plus EBRT (87).

Modern retrospective reviews utilizing HDR brachytherapy have reported similar rates of late Grade 3 GU toxicity ranging from 1% to 14% (88).

Spratt *et al.* analyzed 870 intermediate-risk prostate cancer patients receiving either dose-escalated IMRT to 86.4 Gy or IMRT plus brachytherapy. The authors found that combination therapy resulted in improved biochemical control and distant metastases-free survival. Furthermore, they found that the 7-year actuarial late toxicity rates for Grade 2 gastrointestinal toxicity were 4.6% vs. 4.1% ($p = 0.89$), for Grade 3 gastrointestinal toxicity 0.4% vs. 1.4% ($p = 0.36$), for Grade 2 GU toxicity 19.4% vs. 21.2% ($p = 0.14$), and Grade 3 GU toxicity 3.1% vs. 1.4% ($p = 0.74$) for the IMRT vs. IMRT plus brachytherapy, respectively (8).

Multiple retrospective series have shown that combination therapy results in high rates of ED. However, three large series suggest greater toxicity is not inevitable with combination therapy. Spratt *et al.* (8) reported that there were similar rates of long-term sexual function between IMRT and IMRT plus brachytherapy (mixture of LDR and HDR) with 57.8% of men in the IMRT-alone group and 55.0% in the combination group retaining full potency ($p = 0.67$). Merrick *et al.* (89) reported a dramatic decrease in ED in a large retrospective series when dose was restricted to the penile bulb and infraprostate tissues (90). McLaughlin recently reported no difference in ED at 5 years post–dose-escalated external beam radiotherapy compared to combination therapy when vessel-sparing radiation was employed (91–93). Both series suggest that dose restriction to critical adjacent structures may allow high cure rates and quality of life preservation. The argument against combination therapy is often rooted in the increased rates of GU and sexual toxicity that have been reported in older studies or in ongoing studies that began accruing patients several years ago. As experience with prostate brachytherapy continues to build, imaging and technology improve, and patient selection criteria become more refined, it will become more commonplace to achieve high cure rates without increase in toxicity.

Combined modality vs. surgery

It has proven to be very challenging to compare radiation results to surgical results in high-risk patients. The two modalities have never been compared in a prospective randomized trial. The rationale for surgery in high-risk patients is not based on excellent results that stand alone, but rather based on comparisons with relatively ineffective beam-only radiation (94–98). Certain studies have suggested improved survival with prostatectomy; however, very few studies have compared "good surgery" to "good radiation" in the era of dose escalation, image guidance, and in conjunction with long-term ADT. Furthermore, the publications that have compared surgery favorably to EBRT are often plagued by differences in patient selection for both modalities and differences in preoperative vs. postoperative staging. These biased studies have even been meta-analyzed by Wallis *et al.* (99), and the results unsurprisingly and inaccurately demonstrate that surgery results in improved survival compared to radiotherapy-treated patients. Ultimately, retrospectively comparing these groups continues to lead to a "self-fulfilling prophecy." It is clear that surgical patients and radiation patients are different (radiation patients are older, have more comorbidities, and worse prognostic features), and there are too many unaccounted for variables to correct for on a multivariable analysis or matched pair analysis with propensity scoring. Additionally, variations in the definition of failure, followup, use of salvage therapies, and duration and use of ADT further confound these analyses. Thus, any nonrandomized comparisons will continue to lead to the unavoidable and false self-fulfilling prophecy that surgery yields improved outcomes over radiotherapy.

To elicit an unbiased understanding of contemporary surgical outcomes in patients with high-risk prostate cancer, we performed an extensive literature review of surgical series that focused strictly on clinically staged patients treated primarily with surgery alone (Table 1). Thirteen articles were identified that reported surgical outcomes on clinically staged high-risk patients. Rates of bRFS at 10 year ranged from 27% to 55% (14,55,76–82,100–102). This is consistent with the results from commonly used nomograms, such as the Memorial Sloan Kettering Nomogram. In a recent publication, Abdollah *et al.* (76) sought to better delineate this spectrum. This modern era paper reports long-term outcomes of 1100 high-risk patients treated with robotic prostatectomies with or without pelvic lymph node dissections at tertiary centers between 2002 and 2013. Approximately 50% of these patients had a clinical stage of T2a or less, and 70% had a PSA of 10 or less, which comprises a favorable high-risk population. Less than 5% received adjuvant treatment with either radiation or hormone therapy. BRFS in the cohort overall at 10 years was 50%, and clinical recurrence-free survival at 10 years was 87%. In those patients with a GS of 8 or greater and a PSA of 10 or less, bRFS averaged 36% and clinical recurrence-free survival averaged 85%. Recently, Kishan *et al.* published a multi-institutional analysis comparing outcomes in 487 patients with Gleason 9–10 disease treated with EBRT, CMRT, or Surgery. The patients managed with radiation were older, with higher PSAs, and higher clinical stage. Of the surgical patients, 12% received adjuvant radiation. The 10-year DMFS was highest in the CMRT patients at 90% compared to 67% for EBRT ($p = 0.0008$) patients and 62% for surgery patients ($p = 0.0003$) (103).

A direct comparison of surgery followed by adjuvant radiotherapy to combination brachytherapy is necessary to determine the optimal treatment paradigm for achieving the best cure rate and preserving quality of life. However, until such a study is done and until adjuvant radiation is regularly implemented after surgery for high-risk prostate cancer patients, the current state of evidence suggests that brachytherapy-based combination therapy provides the most durable control of disease.

Conclusions

The most common site of failure for men with high-risk disease treated with external beam radiotherapy is local (104). In multiple contexts, the intensification of local therapy (adjuvant radiotherapy after surgery or radiosensitization to improve local control with ADT) has demonstrated reductions in distant metastases and improvements in overall survival. Recently, the ASCENDE-RT study has shown impressive biochemical control benefits with the addition of a third way to intensify local therapy—the addition of a brachytherapy boost to external beam radiotherapy. Although followup is short, it is highly plausible that comparable benefits will be seen in distant metastases and overall survival as this trial matures.

Just as the use of adjuvant radiotherapy or ADT results in incrementally increased side effects, and early declines in quality of life, the addition of supplemental brachytherapy has also shown incremental increase in side effects. However, brachytherapy is highly operator dependent, and excellent quality of life outcomes have been demonstrated from high-quality implants using modern imaging and treatment planning techniques. Future comparisons of surgical outcomes and radiotherapy must include men treated with combination therapy instead of the current practice of comparing surgery with external beam often without ADT. Given the high recurrence rate after surgery alone or external beam radiotherapy alone for men with high-risk prostate cancer, the use of ADT and the strong consideration for the addition of brachytherapy should be viewed as the gold standard treatment approach today.

References

[1] Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. *CA Cancer J Clin* 2015;65:5–29.

[2] Riihimäki M, Thomsen H, Brandt A, *et al*. What do prostate cancer patients die of? *Oncologist* 2011;16:175–181.

[3] Mohler J, Armstrong A, Bahnson R. *NCCN Clinical Practice Guidelines for Prostate cancer [Internet]* 2015.

[4] Zumsteg ZS, Spratt DE, Pei I, *et al*. A new risk classification system for therapeutic decision making with intermediate-risk prostate cancer patients undergoing dose-escalated external-beam radiation therapy. *Eur Urol* 2013;64:895–902.

[5] Hernandez DJ, Nielsen ME, Han M, *et al*. Contemporary evaluation of the D'Amico risk classification of prostate cancer. *Urology* 2007;70:931–935.

[6] Spratt DE, Zumsteg Z, Ghadjar P, *et al*. Prognostic importance of Gleason 7 disease among patients treated with external beam radiation therapy for prostate cancer: Results of a detailed biopsy core analysis. *Int J Radiat Oncol Biol Phys* 2013;85:1254–1261.

[7] Spratt DE, Pei X, Yamada J, *et al*. Long-term survival and toxicity in patients treated with high-dose intensity modulated radiation therapy for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2013;85:686–692.

[8] Spratt DE, Zumsteg ZS, Ghadjar P, *et al*. Comparison of high-dose (86.4 Gy) IMRT vs combined brachytherapy plus IMRT for intermediate-risk prostate cancer. *BJU Int* 2014;114:360–367.

[9] Cooperberg MR, Lubeck DP, Mehta SS, *et al*. Time trends in clinical risk stratification for prostate cancer: Implications for outcomes (data from CaPSURE). *J Urol* 2003;170:S21–S27.

[10] Rubin R. Researchers look to MRI and biomarkers to help improve detection of aggressive prostate cancers. *JAMA* 2015;313:654–656.

[11] Osborne JR, Green DA, Spratt DE, *et al*. A prospective pilot study of 89 Zr-J591/prostate specific membrane antigen positron emission tomography in men with localized prostate cancer undergoing radical prostatectomy. *J Urol* 2014;191:1439–1445.

[12] Jackson W, Hamstra DA, Johnson S, *et al*. Gleason pattern 5 is the strongest pathologic predictor of recurrence, metastasis, and prostate cancer-specific death in patients receiving salvage radiation therapy following radical prostatectomy. *Cancer* 2013;119:3287–3294.

[13] Sabolch A, Feng FY, Daignault-Newton S, *et al*. Gleason pattern 5 is the greatest risk factor for clinical failure and death from prostate cancer after dose-escalated radiation therapy and hormonal ablation. *Int J Radiat Oncol Biol Phys* 2011;81:e351–e360.

[14] Ellis CL, Partin AW, Han M, *et al*. Adenocarcinoma of the prostate with Gleason score 9-10 on core biopsy: Correlation with findings at radical prostatectomy and prognosis. *J Urol* 2013;190:2068–2073.

[15] Zelefsky MJ, Kollmeier M, Cox B, *et al*. Improved clinical outcomes with high-dose image guided radiotherapy compared with non-IGRT for the treatment of clinically localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2012;84:125–129.

[16] Sandler HM, Hu C, Rosenthal SA, et al. A phase III protocol of androgen suppression (AS) and 3DCRT/IMRT versus AS and 3DCRT/IMRT followed by chemotherapy (CT) with docetaxel and prednisone for localized, high-risk prostate cancer (RTOG 0521). ASCO Annual Meeting Proceedings 2015. p. LBA5002.

[17] Jones CU, Hunt D, McGowan DG, *et al*. Radiotherapy and short-term androgen deprivation for localized prostate cancer. *N Engl J Med* 2011;365:107–118.

[18] Warde P, Mason M, Ding K, *et al*. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: A randomised, phase 3 trial. *Lancet* 2011;378:2104–2111.

[19] Polkinghorn WR, Parker JS, Lee MX, *et al*. Androgen receptor signaling regulates DNA repair in prostate cancers. *Cancer Discov* 2013;3:1245–1253.

[20] Spratt DE, Evans MJ, Davis BJ, *et al*. Androgen receptor upregulation mediates radioresistance after ionizing radiation. *Cancer Res* 2015;75:4688–4696.

[21] Barrett T, Gill AB, Kataoka MY, *et al*. DCE and DW MRI in monitoring response to androgen deprivation therapy in patients with prostate cancer: A feasibility study. *Magn Reson Med* 2012;67:778–785.

[22] Kim AY, Kim CK, Park SY, *et al*. Diffusion-weighted imaging to evaluate for changes from androgen deprivation therapy in prostate cancer. *AJR Am J Roentgenol* 2014;203:W645–W650.

[23] Thompson IM, Tangen CM, Paradelo J, *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;181:956–962.

[24] Critz FA, Levinson K. 10-year disease-free survival rates after simultaneous irradiation for prostate cancer with a focus on calculation methodology. *J Urol* 2004;172:2232–2238.

[25] Sylvester JE, Grimm PD, Blasko JC, *et al*. 15-Year biochemical relapse free survival in clinical stage T1-T3 prostate cancer following combined external beam radiotherapy and brachytherapy; Seattle experience. *Int J Radiat Oncol Biol Phys* 2007;67:57–64.

[26] McLaughlin PW, Narayana V. High-dose-rate strictures: A theory of cancer meets anatomic reality. *Brachytherapy* 2013;12:199–201.

[27] Stock RG, Stone NN, Tabert A, *et al*. A dose-response study for I-125 prostate implants. *Int J Radiat Oncol Biol Phys* 1998;41:101–108.

[28] Potters L, Cao Y, Calugaru E, *et al*. A comprehensive review of CT-based dosimetry parameters and biochemical control in patients treated with permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2001;50:605–614.

[29] Butler WM, Stewart RR, Merrick GS. A detailed radiobiological and dosimetric analysis of biochemical outcomes in a case-control study of permanent prostate brachytherapy patients. *Med Phys* 2009;36:776–787.
[30] Butler WM, Stewart RR, Merrick GS. Evaluation of radiobiologic biochemical control in a large permanent prostate brachytherapy population from a single institution using AAPM TG-137 parameters. *Brachytherapy* 2011;10:16–28.
[31] Miles EF, Nelson JW, Alkaissi AK, *et al*. Biologically effective dose (BED) correlation with biochemical control after low-dose rate prostate brachytherapy for clinically low-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2010;77:139–146.
[32] Stone NN, Potters L, Davis BJ, *et al*. Multicenter analysis of effect of high biologic effective dose on biochemical failure and survival outcomes in patients with Gleason score 7-10 prostate cancer treated with permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2009;73:341–346.
[33] Stone NN, Stock RG, Cesaretti JA, *et al*. Local control following permanent prostate brachytherapy: Effect of high biologically effective dose on biopsy results and oncologic outcomes. *Int J Radiat Oncol Biol Phys* 2010;76:355–360.
[34] Vogelius IR, Bentzen SM. Meta-analysis of the alpha/beta ratio for prostate cancer in the presence of an overall time factor: Bad news, good news, or no news? *Int J Radiat Oncol Biol Phys* 2013;85:89–94.
[35] Hindson BR, Millar JL, Matheson B. Urethral strictures following high-dose-rate brachytherapy for prostate cancer: Analysis of risk factors. *Brachytherapy* 2013;12:50–55.
[36] Ménard C, Susil RC, Choyke P, *et al*. MRI-guided HDR prostate brachytherapy in standard 1.5T scanner. *Int J Radiat Oncol Biol Phys* 2004;59:1414–1423.
[37] Morton GC, Hoskin PJ. Brachytherapy: Current status and future strategies—can high dose rate replace low dose rate and external beam radiotherapy? *Clin Oncol (R Coll Radiol)* 2013;25:474–482.
[38] Martinez AA, Gonzalez J, Ye H, *et al*. Dose escalation improves cancer-related events at 10 years for intermediate- and high-risk prostate cancer patients treated with hypofractionated high-dose-rate boost and external beam radiotherapy. *Int J Radiat Oncol Biol Phys* 2011;79:363–370.
[39] Kaprealian T, Weinberg V, Speight JL, *et al*. High-dose-rate brachytherapy boost for prostate cancer: Comparison of two different fractionation schemes. *Int J Radiat Oncol Biol Phys* 2012;82:222–227.
[40] Hoskin PJ, Rojas AM, Bownes PJ, *et al*. Randomised trial of external beam radiotherapy alone or combined with high-dose-rate brachytherapy boost for localised prostate cancer. *Radiother Oncol* 2012;103:217–222.
[41] Bachand F, Martin AG, Beaulieu L, *et al*. An eight-year experience of HDR brachytherapy boost for localized prostate cancer: Biopsy and PSA outcome. *Int J Radiat Oncol Biol Phys* 2009;73:679–684.
[42] Aström L, Pedersen D, Mercke C, *et al*. Long-term outcome of high dose rate brachytherapy in radiotherapy of localised prostate cancer. *Radiother Oncol* 2005;74:157–161.
[43] Galalae RM, Martinez A, Mate T, *et al*. Long-term outcome by risk factors using conformal high-dose-rate brachytherapy (HDR-BT) boost with or without neoadjuvant androgen suppression for localized prostate cancer. *Int J Radiat Oncol Biol Phys* 2004;58:1048–1055.
[44] Galalae RM, Zakikhany NH, Geiger F, *et al*. The 15-year outcomes of high-dose-rate brachytherapy for radical dose escalation in patients with prostate cancer—a benchmark for high-tech external beam radiotherapy alone? *Brachytherapy* 2014;13:117–122.
[45] Demanes DJ, Rodriguez RR, Schour L, *et al*. High-dose-rate intensity-modulated brachytherapy with external beam radiotherapy for prostate cancer: California endocurietherapy's 10-year results. *Int J Radiat Oncol Biol Phys* 2005;61:1306–1316.
[46] Prada PJ, González H, Fernández J, *et al*. Biochemical outcome after high-dose-rate intensity modulated brachytherapy with external beam radiotherapy: 12 years of experience. *BJU Int* 2012;109:1787–1793.
[47] Viani GA, Pellizzon AC, Guimarães FS, *et al*. High dose rate and external beam radiotherapy in locally advanced prostate cancer. *Am J Clin Oncol* 2009;32:187–190.
[48] Davis BJ, Horwitz EM, Lee WR, *et al*. American Brachytherapy Society consensus guidelines for transrectal ultrasound-guided permanent prostate brachytherapy. *Brachytherapy* 2012;11:6–19.
[49] Yamada Y, Rogers L, Demanes DJ, *et al*. American Brachytherapy Society consensus guidelines for high-dose-rate prostate brachytherapy. *Brachytherapy* 2012;11:20–32.
[50] Bittner N, Merrick GS, Butler WM, *et al*. Gleason score 7 prostate cancer treated with interstitial brachytherapy with or without supplemental external beam radiation and androgen deprivation therapy: Is the primary pattern on needle biopsy prognostic? *Brachytherapy* 2013;12:14–18.
[51] Fang LC, Merrick GS, Butler WM, *et al*. High-risk prostate cancer with Gleason score 8-10 and PSA level ≤15 ng/mL treated with permanent interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2011;81:992–996.
[52] Merrick GS, Butler WM, Galbreath RW, *et al*. Relationship between percent positive biopsies and biochemical outcome after permanent interstitial brachytherapy for clinically organ-confined carcinoma of the prostate gland. *Int J Radiat Oncol Biol Phys* 2002;52:664–673.
[53] Taira AV, Merrick GS, Galbreath RW, *et al*. Long-term outcomes of prostate cancer patients with Gleason pattern 5 treated with combined brachytherapy and external beam radiotherapy. *Brachytherapy* 2013;12:408–414.
[54] Bittner N, Merrick GS, Galbreath RW, *et al*. Treatment outcomes with permanent brachytherapy in high-risk prostate cancer patients stratified into prognostic categories. *Brachytherapy* 2015;14:766–772.
[55] Joniau S, Briganti A, Gontero P, *et al*. Stratification of high-risk prostate cancer into prognostic categories: A European multi-institutional study. *Eur Urol* 2015;67:157–164.
[56] Shilkrut M, Merrick GS, McLaughlin PW, *et al*. The addition of low-dose-rate brachytherapy and androgen-deprivation therapy decreases biochemical failure and prostate cancer death compared with dose-escalated external-beam radiation therapy for high-risk prostate cancer. *Cancer* 2013;119:681–690.
[57] Liss AL, Abu-Isa EI, Jawad MS, *et al*. Combination therapy improves prostate cancer survival for patients with potentially lethal prostate cancer: The impact of Gleason pattern 5. *Brachytherapy* 2015;14:502–510.
[58] Stock RG, Cesaretti JA, Hall SJ, *et al*. Outcomes for patients with high-grade prostate cancer treated with a combination of brachytherapy, external beam radiotherapy and hormonal therapy. *BJU Int* 2009;104:1631–1636.
[59] Keyes M. *ASCENDE-rt trial update and future directions in high risk disease. The utilization of MRI in LDR and HDR prostate brachytherapy: from diagnostics to response assessment*. Houston, TX: MD Anderson Cancer Center; 2015.
[60] Marshall RA, Buckstein M, Stone NN, *et al*. Treatment outcomes and morbidity following definitive brachytherapy with or without external beam radiation for the treatment of localized prostate cancer: 20-year experience at Mount Sinai Medical Center. *Urol Oncol* 2014;32:38.e1–38.e7.
[61] Merrick GS, Butler WM, Galbreath RW, *et al*. Prostate cancer death is unlikely in high-risk patients following quality permanent interstitial brachytherapy. *BJU Int* 2011;107:226–232.
[62] Taira AV, Merrick GS, Butler WM, *et al*. Long-term outcome for clinically localized prostate cancer treated with permanent interstitial brachytherapy. *Int J Radiat Oncol Biol Phys* 2011;79:1336–1342.
[63] Dattoli M, Wallner K, True L, *et al*. Long-term outcomes for patients with prostate cancer having intermediate and high-risk

disease, treated with combination external beam irradiation and brachytherapy. *J Oncol* 2010;2010. 471375.
[64] Bittner N, Merrick GS, Galbreath RW, *et al*. Primary causes of death after permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2008;72:433–440.
[65] Johnson J, Roach M, Gottschalk A, *et al*. (P070) high-risk prostate adenocarcinoma treated with whole-pelvis radiotherapy HDR brachytherapy boost results in very high disease-specific survival. *Oncology (Williston Park)* 2015;29(4 Suppl 1).
[66] Savdie R, Symons J, Spernat D, *et al*. High-dose rate brachytherapy compared with open radical prostatectomy for the treatment of high-risk prostate cancer: 10 year biochemical freedom from relapse. *BJU Int* 2012;110 Suppl 4:71–76.
[67] Krauss D, Kestin L, Ye H, *et al*. Lack of benefit for the addition of androgen deprivation therapy to dose-escalated radiotherapy in the treatment of intermediate- and high-risk prostate cancer. *Int J Radiat Oncol Biol Phys* 2011;80:1064–1071.
[68] Martinez A, Shah C, Mohammed N, *et al*. Ten-year outcomes for prostate cancer patients with Gleason 8 through 10 with external beam radiation and high-dose-rate brachytherapy boost in the PSA era. *J Radiat Oncol* 2016;5:87–93.
[69] Dearnaley DP, Jovic G, Syndikus I, *et al*. Escalated-dose versus control-dose conformal radiotherapy for prostate cancer: Long-term results from the MRC RT01 randomised controlled trial. *Lancet Oncol* 2014;15:464–473.
[70] Stenmark MH, Blas K, Halverson S, *et al*. Continued benefit to androgen deprivation therapy for prostate cancer patients treated with dose-escalated radiation therapy across multiple definitions of high-risk disease. *Int J Radiat Oncol Biol Phys* 2011;81:e335–e344.
[71] Zelefsky MJ, Yamada Y, Kollmeier MA, *et al*. Long-term outcome following three-dimensional conformal/intensity-modulated external-beam radiotherapy for clinical stage T3 prostate cancer. *Eur Urol* 2008;53:1172–1179.
[72] Kuban DA, Tucker SL, Dong L, *et al*. Long-term results of the M. D. Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys* 2008;70:67–74.
[73] Wiegel T, Bartkowiak D, Bottke D, *et al*. Adjuvant radiotherapy versus wait-and-see after radical prostatectomy: 10-year follow-up of the ARO 96-02/AUO AP 09/95 trial. *Eur Urol* 2014;66:243–250.
[74] Bolla M, van Poppel H, Tombal B, *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;380:2018–2027.
[75] Swanson GP, Thompson IM. Adjuvant radiotherapy for high-risk patients following radical prostatectomy. *Urol Oncol* 2007;25:515–519.
[76] Abdollah F, Sood A, Sammon JD, *et al*. Long-term cancer control outcomes in patients with clinically high-risk prostate cancer treated with robot-assisted radical prostatectomy: Results from a multi-institutional study of 1100 patients. *Eur Urol* 2015;68:497–505.
[77] Briganti A, Joniau S, Gontero P, *et al*. Identifying the best candidate for radical prostatectomy among patients with high-risk prostate cancer. *Eur Urol* 2012;61:584–592.
[78] Yamamoto S, Kawakami S, Yonese J, *et al*. Long-term oncological outcome and risk stratification in men with high-risk prostate cancer treated with radical prostatectomy. *Jpn J Clin Oncol* 2012;42:541–547.
[79] Loeb S, Schaeffer EM, Trock BJ, *et al*. What are the outcomes of radical prostatectomy for high-risk prostate cancer? *Urology* 2010;76:710–714.
[80] Inman BA, Davies JD, Rangel LJ, *et al*. Long-term outcomes of radical prostatectomy with multimodal adjuvant therapy in men with a preoperative serum prostate-specific antigen level > or =50 ng/mL. *Cancer* 2008;113:1544–1551.
[81] Bastian PJ, Gonzalgo ML, Aronson WJ, *et al*. Clinical and pathologic outcome after radical prostatectomy for prostate cancer patients with a preoperative Gleason sum of 8 to 10. *Cancer* 2006;107:1265–1272.
[82] Ward JF, Slezak JM, Blute ML, *et al*. Radical prostatectomy for clinically advanced (cT3) prostate cancer since the advent of prostate-specific antigen testing: 15-year outcome. *BJU Int* 2005;95:751–756.
[83] Sathya JR, Davis IR, Julian JA, *et al*. Randomized trial comparing iridium implant plus external-beam radiation therapy with external-beam radiation therapy alone in node-negative locally advanced cancer of the prostate. *J Clin Oncol* 2005;23:1192–1199.
[84] Morris W. Is ASCENDE-RT still pertinent? Is LDR-PB obsolete?. Available at: https://www.prostatebrachytherapy.org.uk/2016-presentations/J-Morris%20170516.pdf2016. Accessed July 20, 2016.
[85] Demanes DJ, Brandt D, Schour L, *et al*. Excellent results from high dose rate brachytherapy and external beam for prostate cancer are not improved by androgen deprivation. *Am J Clin Oncol* 2009;32:342–347.
[86] Chan EK, Keyes M, Pickles T, *et al*. Decline in acute urinary toxicity: A long-term study in 2011 patients with prostate brachytherapy within a provincial institution. *Brachytherapy* 2014;13:46–52.
[87] Buckstein M, Carpenter TJ, Stone NN, *et al*. Long-term outcomes and toxicity in patients treated with brachytherapy for prostate adenocarcinoma younger than 60 years of age at treatment with minimum 10 years of follow-up. *Urology* 2013;81:364–368.
[88] Morton GC. High-dose-rate brachytherapy boost for prostate cancer: Rationale and technique. *J Contemp Brachytherapy* 2014;6:323–330.
[89] Merrick GS, Butler WM, Wallner KE, *et al*. Erectile function after prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2005;62:437–447.
[90] Taira AV, Merrick GS, Galbreath RW, *et al*. Erectile function durability following permanent prostate brachytherapy. *Int J Radiat Oncol Biol Phys* 2009;75:639–648.
[91] Liss AL, Evans C, Narayana V, *et al*. *Comparison of external beam and combination therapy for prostate cancer: patient-reported outcomes of sexual function with 5-year follow-up*. San Francisco: American Society of Radiation Oncology (ASTRO); 2014. p. S54.
[92] McLaughlin PW, Narayana V, Meirovitz A, *et al*. Vessel-sparing prostate radiotherapy: Dose limitation to critical erectile vascular structures (internal pudendal artery and corpus cavernosum) defined by MRI. *Int J Radiat Oncol Biol Phys* 2005;61:20–31.
[93] Lee JY, Spratt DE, Liss AL, *et al*. Vessel-sparing radiation and functional anatomy-based preservation for erectile function after prostate radiotherapy. *Lancet Oncol* 2016;17:e198–e208.
[94] Cooperberg MR, Vickers AJ, Broering JM, *et al*. Comparative risk-adjusted mortality outcomes after primary surgery, radiotherapy, or androgen-deprivation therapy for localized prostate cancer. *Cancer* 2010;116:5226–5234.
[95] Hoffman RM, Koyama T, Fan KH, *et al*. Mortality after radical prostatectomy or external beam radiotherapy for localized prostate cancer. *J Natl Cancer Inst* 2013;105:711–718.
[96] Kibel AS, Ciezki JP, Klein EA, *et al*. Survival among men with clinically localized prostate cancer treated with radical prostatectomy or radiation therapy in the prostate specific antigen era. *J Urol* 2012;187:1259–1265.
[97] Nepple KG, Stephenson AJ, Kallogjeri D, *et al*. Mortality after prostate cancer treatment with radical prostatectomy, external-beam radiation therapy, or brachytherapy in men without comorbidity. *Eur Urol* 2013;64:372–378.
[98] Sooriakumaran P, Nyberg T, Akre O, *et al*. Comparative effectiveness of radical prostatectomy and radiotherapy in prostate cancer: Observational study of mortality outcomes. *BMJ* 2014;348:g1502.

[99] Wallis CJ, Saskin R, Choo R, *et al*. Surgery versus radiotherapy for clinically-localized prostate cancer: A systematic review and meta-analysis. *Eur Urol* 2016;70:21–30.

[100] Carver BS, Bianco FJ, Scardino PT, *et al*. Long-term outcome following radical prostatectomy in men with clinical stage T3 prostate cancer. *J Urol* 2006;176:564–568.

[101] Do TM, Parker RG, Smith RB, *et al*. High-grade carcinoma of the prostate: A comparison of current local therapies. *Urology* 2001;57:1121–1126. discussion 6–7.

[102] Schreiber D, Rineer J, Weiss JP, *et al*. Clinical and biochemical outcomes of men undergoing radical prostatectomy or radiation therapy for localized prostate cancer. *Radiat Oncol J* 2015;33:21–28.

[103] Kishan AU, Shaikh T, Wang PC, *et al*. Clinical outcomes for patients with Gleason score 9-10 prostate adenocarcinoma treated with radiotherapy or radical prostatectomy: A multi-institutional comparative analysis. *Eur Urol* 2016; http://dx.doi.org/10.1016/j.eururo.2016.06.046. [Epub ahead of print].

[104] Zumsteg ZS, Spratt DE, Romesser PB, *et al*. Anatomical patterns of recurrence following biochemical relapse in the dose escalation era of external beam radiotherapy for prostate Cancer. *J Urol* 2015;194:1624–1630.