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Concurrent chemoradiation for high-risk prostate cancer

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Abstract

There are estimated to be 220800 cases of prostate cancer diagnosed in 2015, making up 26% of all cancer diagnoses. Fortunately, adenocarcinoma of the prostate is often a highly treatable malignancy. Even though the majority of prostate cancer patients present with localized disease, prostate cancer still accounts for over 27000 deaths a year. There is a subset of patients that are likely to recur after locoregional treatment that is thought of as a "high-risk" population. This more aggressive subset includes patients with clinical stage greater than T2b, Gleason score greater than 7, and prostate specific antigen greater than 20 ng/dL. The rate of biochemical relapse in this high risk group is 32%-70% within five years of definitive focal therapy. Given these discouraging outcomes, attempts have been made to improve cure rates by radiation dose escalation, addition of androgen depravation therapy, and addition of chemotherapy either sequentially or concurrently with radiation. One method that has been shown to improve clinical outcomes is the addition of chemotherapy to radiotherapy for definitive treatment. Concurrent chemoradiation with 5-fluorouracil, estramustine phosphate, vincristine, docetaxel, and paclitaxel has been studied in the phase I and/or II setting. These trials have identified the maximum tolerated dose of chemotherapy and radiation that can be safely delivered concurrently and established the safety and feasibility of this technique. This review will focus on the addition of concurrent chemotherapy to radiotherapy in the definitive management of high-risk prostate cancer.

Key words: Prostate cancer; Chemoradiation; High-risk prostate cancer; Concurrent chemotherapy; Chemotherapy; Intensity modulated radiation therapy

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Core tip: Over half of patients with high-risk prostate cancer will have a biochemical relapse within 5 years when treated primarily with radiotherapy as shown in multiple studies. One method that has been shown to improve local control, and in some disease sites overall survival, is the addition of chemotherapy to radiotherapy for definitive treatment. We review the safety and efficacy data of combined chemoradiation in patients with high risk adenocarcinoma of the prostate.

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INTRODUCTION

Prostate cancer is the leading non-cutaneous oncologic diagnosis in males with an estimated 220800 cases to be diagnosed in 2015, making up 26% of all cancer diagnoses and leading to over 27000 deaths[1]. While adenocarcinoma of the prostate is often thought of as a relatively indolent malignancy, disease presentation and clinical outcome are often quite heterogeneous. Even though the majority of prostate cancer patients are diagnosed with localized disease, there is a subset of patients that are likely to recur after locoregional treatment that is thought of as a "high-risk" population. Disease characteristics that portend a more aggressive phenotype and place patients in a high-risk category are clinical stage greater than T2b, Gleason score greater than 7, and prostate specific antigen (PSA) greater than 20 ng/dL[2]. Patients in this high risk group have a biochemical relapse rate of 32%-70% five years following definitive focal therapy[2-8].

Given these discouraging results, efforts have been made to improve outcomes by radiation dose escalation. Early results in the setting of advanced disease were only available from centers with proton beam radiation therapy (RT), such as Harvard University, due to gastrointestinal (GI) and genitourinary(GU) toxicity associated with higher radiation doses delivered with less focused radiation techniques[9,10]. Patients with T3-4, Nx-2, M0 prostate cancer were randomly assigned to radiation to the whole pelvis *via* a 4-field box technique to 50.4 Gy, followed by a photon (16.8 Gy) or proton (25.2 CGE) boost. There was an improvement in local control only in patients with high Gleason score with dose escalation and a 8-year failure rate of 23% in the entire cohort[11]. The advent of computed tomography based planning allowed for radiation doses above 70 Gy to be delivered safely with three dimensional conformal radiation therapy (3D-CRT)[12]. A prospective, 3D-CRT dose escalation study mandating sextant prostate biopsy after treatment demonstrated a 7% positive biopsy rate after doses of 81 Gy *vs* 57% positivity in patients receiving 64.8 Gy. Despite this low biopsy rate, patients with 2 or more high risk features (T-stage > 2, pretreatment PSA > 10.0 ng/dL and Gleason score > 6) had a 65% chance of PSA failure[13].

Another strategy to augment cure rates is the addition of androgen deprivation therapy (ADT) to radiation therapy. EORTC 22863, a multi-intuitional randomized trial of 415 patients testing RT alone *vs* RT + ADT (concurrently and adjuvantly for 3 years) demonstrated a 16% overall survival benefit supporting the strategy of combined ADT and RT[14]. However, RTOG 86-10 testing neoadjuvant and concurrent ADT (4 mo total) *vs* RT alone did not demonstrate an overall survival benefit in 471 patients[15]. Furthermore, the biochemical failure rate at 10 years was 65% in the combined treatment arm of RTOG 86-10.

These uninspiring results demonstrate the need for better treatment options in patients with high-risk prostate cancer. One method that has been shown to improve local control, and in some disease sites overall survival, is the addition of chemotherapy to RT for definitive therapy[16-25]. This review will focus on the addition of concurrent chemotherapy to radiation therapy in the definitive management of high-risk prostate cancer.

EARLY EXPERIENCE WITH CONCURRENT 5-FLUOROURACIL

Drawing on over 30 years of experience from the treatment of adenocarcinoma of the gastrointestinal tract[26] and *in vitro* evidence that 5-fluorouracil (5-FU) is a radiosensitizer in DU-145 human prostate cell lines[27,28], the Southwest Oncology Group (SWOG 9024) initiated a phase Ⅱ trial testing chemoradiation with 5-FU in locally advanced prostate cancer[29]. Patients were included if they were cT3 or greater and node negative/metastasis free. Patients were treated with a 4-field approach to 45 Gy followed by a CT-defined boost to the prostate and seminal vesicles to a total dose of 70.2 Gy in 39 fractions. Continuous infusion 5-FU at a dose of 200 mg/m^2 daily was administered from day 1 until the completion of radiotherapy. Thirty eligible patients were accrued from 1991 to 1993 with 13 patients achieving a PSA < 1.0 ng/dL with 6 of these 13 patients also having a negative post-treatment biopsy. Seven patients had grade 3 toxicity and 2 had grade 4 toxicity, but no toxicity necessitated a treatment break. The most common toxicity was diarrhea with 2 patients having grade 3 and 1 patient having grade 4 acute toxicity. While the results of this trial were not overly encouraging, the demonstration that chemotherapy could be combined with radiotherapy to 70.2 Gy with acceptable toxicity paved the way for future trials combining chemotherapy and radiation.

CONCURRENT AND NEOADJUVANT PLUS CONCURRENT ESTRAMUSTINE PHOSPHATE

Estramustine Phosphate (EP) is a cytotoxic agent that binds to microtubule associated proteins and inhibits spindle formation[30]. This results in G_2 phase arrest and accumulation of cells in the radiosensitive G_2/M phase of the cell cycle[31]. For this reason EP was tested as a radiosensitizer both *in vivo* and clinically and found to have an enhancement ratio of 1.3-1.6[32,33]. Vinblastine, another microtubule inhibiting agent[34], when combined with EP has led to tumor regression in patients with

hormone-refractory, metastatic prostate cancer[35] and was therefore a logical doublet (EV) to test in the concurrent setting. EV and concurrent RT was first tested by Khil *et al*[36] in 65 patients between 1991 and 1996 with either: cT2b-c and Gleason Score 9-10, cT3, or cTxN1M0 prostate cancer. Patients were treated with EP at 450 mg/m^2 by mouth daily with a weekly infusion of vinblastine (3 mg/m^2) and concurrent whole pelvis conventional radiation to 45 Gy followed by a prostate boost of 20-25 Gy. Patient Gleason score ranged from 4-10 and pretreatment PSA was defined in cohorts of less than 20 (32%), 20 to 50 (35%) and greater than 50 (32%). Six weeks following the completion of chemoradiation all patients had a complete response on rectal exam. With a median follow-up of 43 mo, 86% of patients had an undetectable PSA at nadir and 48% remained in biochemical remission. Clinical control was achieved in 81% of the patients. Biochemical relapse free survival was 49%, 38% and 17% for patients with stage T2, T3 and T4 disease, respectively. Furthermore, biochemical relapse free survival was 60% or greater in patients with a PSA $\leqslant$ 50 ng/dL compared to 0% in the patients with a PSA greater than 50 ng/dL, highlighting the importance of disease burden at diagnosis on response[36].

This study on EV combined with radiation therapy lent evidence for initiating a phase Ⅱ study at Memorial Sloan-Kettering Cancer Center published initially in 2000[37]. The impetus for this study was to combine EV with high-dose 3DCRT (75.6 Gy). Patients with the following 5 clinical scenarios were included: (1) Gleason score $\geqslant$ 8 and PSA > 10 ng/dL; (2) Gleason score of 7 and PSA > 20 ng/dL; (3) cT3 and PSA > 20; (4) cT4; or (5) cTxN1M0. Estramustine was given by mouth daily at 10 mg/kg in three divided doses with two neoadjuvant 8-wk cycles of intravenous vinblastine (weekly as 4 mg/m^2) followed by 8 wk of concomitant EV and high-dose 3DCRT. Twenty seven patients were enrolled from 1996 to 1998 and 2 patients could not tolerate the entire treatment course due to liver dysfunction likely secondary to EP. Acute grade 3 GI and GU toxicity was observed in 35% and 48% of patients, respectively. Late toxicity was uncommon with no grade 3 or greater GI toxicity, and only 12% grade 3 GU toxicity. The efficacy was reported in a follow-up manuscript in 2004 with a 34% 5-year biochemical free survival in patients who tolerated the entire treatment regimen at a median follow-up of 5 years[38]. The median time to PSA failure was 1 year with 22% of patients developing metastases. There were no severe long-term toxicities and 48% of patients received no further therapy, supporting neoadjuvant and concurrent EV as a viable alternative to ADT.

There was a similar, contemporaneous pilot study accruing from 1996 to 1999 which was reported by Ben-Josef *et al*[39] in 2001. Patients were eligible if they had cT3-4 or cT1c-2c prostate cancer with a Gleason score > 7 and a serum PSA > 15 ng/dL. Fourteen of the 16 patients accrued completed the treatment regimen consisting of 2 neoadjuvant 21-d cycles of oral EP (10 mg/kg per day in three divided doses) and oral etoposide (50 mg/m^2 per day, in two divided doses), followed by concurrent EP (10 mg/kg per day, PO) and 3DCRT (70.2 Gy). Etoposide resulted in temporary epilation in all patients. With a median follow-up of only 20 mo, 5 of 7 assessable patients demonstrated biopsy negative disease. Actuarial overall survival and disease-free survival at three years were 88% and 73%, respectively. Grade 3 toxicity occurred in 3 patients total (19%; hematologic in 2, venous thrombosis in 1). One patient experienced grade 4 cardiac toxicity. Overall, while the follow-up is too short to draw definitive efficacy conclusions, the regimen was relatively well tolerated and warrants further exploration.

TAXANES AS RADIOSENSISTIZERS

Paclitaxel (Taxol), discovered to have anti-tumor activity in the late 1970s, is a diterpenoid isolated from the bark of the Pacific yew, *Taxus brevifolia* and functions as a potent inhibitor of cell replication due to microtubule stabilization[40]. While early clinical studies of the drug were promising[41-43], the slow growth rate of the Pacific yew tree and resulting tree death upon Taxol extraction made extraction in quantities sufficient for large scale clinical trials difficult. This clinical need lead researchers at multiple institutes in France to prepare the semisynthetic Taxol derivative docetaxel (Taxotere/Docedad)[44,45]. Because of the ability of docetaxel to stabilize cells in the G_2/M-phase of the cell cycle, docetaxel was tested as, and found to be a radiosensitizer by a factor of 2.5-3.0[46-48]. In the setting of metastatic hormone refractory prostate cancer, docetaxel was demonstrated to be safe and effective in multiple phase Ⅰ and Ⅱ trials[49-51]. The combined systemic efficacy and radiosensitization led researchers to investigate the combination of docetaxel and radiation therapy in patients with high-risk prostate cancer.

The first trial to test the combination of docetaxel and radiation therapy was the phase Ⅰ study by Kumar *et al*[52] conducted from 2000-2002. This docetaxel dose escalation trial tested node negative prostate cancer patients with any of the following advanced features: cT3-4, cT1b-2 and Gleason Score $\geqslant$ 8, or cT1c-2 with Gleason Score 5 to 7 and PSA $\geqslant$ 10 ng/dL. Patients were treated with 3DCRT to a dose of 70.2 Gy in 5 cohorts of docetaxel dosing, ranging from 5-20 mg/m^2. The maximum tolerated dose (MTD) of docetaxel delivered concurrently with radiation was determined to be 20 mg/m^2 with a dose limiting toxicity of diarrhea. One patient required intermittent urinary catheterization for 10 mo after the completion of therapy, which resolved without any surgical intervention. The overall incidence of grade 2 diarrhea and dysuria was 36% and 23%, respectively leading the authors to conclude that this treatment was well tolerated and this regimen should move on to phase Ⅱ testing.

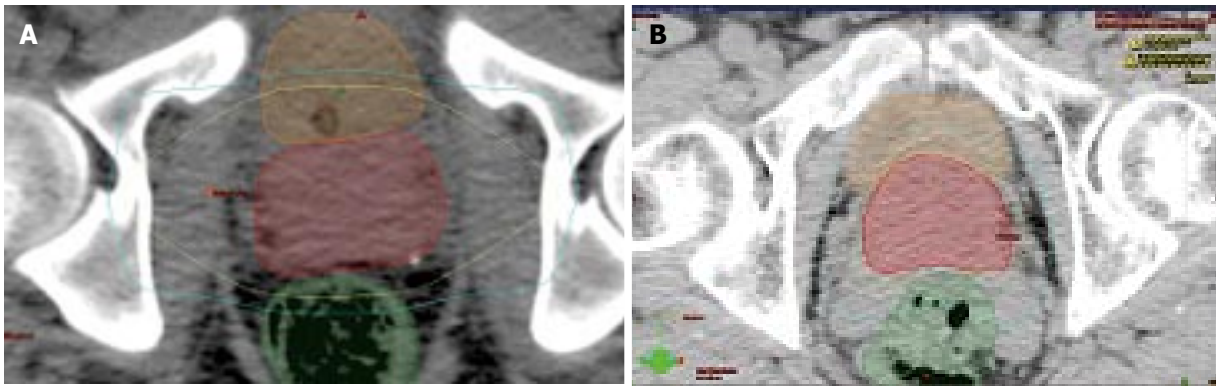

Figure 1 Comparison of three dimensional conformal radiation therapy (A) and intensity modulated radiation therapy (B) treatment plans. The yellow line denotes the area that is receiving the prescription dose. The outer blue line denotes 90% of the prescription dose. Notice in (B) the yellow line conforms to the prostate (red) and does not enter into the bladder or rectum as it does in (A), demonstrating the increased dose given to the bladder and rectum with 3DCRT (A). 3DCRT: Three dimensional conformal radiation therapy.

With the MTC and safety established, a multicenter, phase Ⅱ trial of 50 men with high-risk, locally advanced, or node-positive prostate cancer was conducted between 2003 and 2005[53]. Patients were treated concurrently with 3DCRT to 70 Gy with weekly docetaxel (20 mg/m^2) and a luteinizing hormone-releasing hormone agonist. This was followed by a 3-wk treatment break and three consecutive 21 d cycles of docetaxel (60 mg/m^2). Forty-six of the 50 patients completed full-dose chemoradiation. Treatment was well tolerated with 15 and 5 patients experiencing grade 2 and 3 toxicity, respectively. There were no late grade 3 or greater toxicities. Two-thirds of patients were clinically disease free with a median follow-up of 54 mo with a 5-year survival of 92%. These results are promising and a phase Ⅲ trial is warranted.

With improvements in plant cell fermentation and biosynthesis, paclitaxel production and availability are no longer reliant on the Pacific yew tree and the drug is now widely accessible for clinical use[54]. Paclitaxel, for reasons similar to docetaxel, was found to be a potent radiosensitizer as well[55-59]. Clinical trials of the delivery of chemoradiation using paclitaxel have been efficacious and well tolerated in other malignancies[60-63] leading Sanfilippo *et al*[64] to conduct a phase Ⅰ/Ⅱ trial investigating the use of biweekly paclitaxel in combination with escalating doses of 3DCRT in high-risk prostate cancer patients receiving ADT. Between 2000-2006, 22 patients with cT2-T4 and Gleason score ⩾ 8, PSA > 10 ng/dL, or node-positive disease were treated with biweekly paclitaxel (30 mg/m^2) and escalating doses of 3DCRT (cohorts of 3; 63 Gy, 66.6.Gy, 70.2 Gy, and 73.8 Gy) to determine the MTD of radiation delivered with biweekly paclitaxel. The radiation was initially to be given to the whole pelvis to a dose of 39.6 Gy *via* a 4-field technique followed by a 3DCRT cone-down to the prostate but this was later amended to treat the whole pelvis after the 3DCRT prostate boost after all patients receiving 66.6 Gy had grade 3 diarrhea, in an attempt to limit toxicity. There were subsequently no grade 3 toxicities in the 70.2 Gy cohort and 1 grade 3 toxicity in the 73.8 Gy cohort out of the 6 total patients treated at this dose level. Six of the twenty-two patients experienced a PSA relapse at a median follow-up of 38 mo. The authors concluded that combined chemoradiation with paclitaxel is safe and effective and they suggested a MTD of 73.8 Gy when using 3DCRT.

CONCURRENT CHEMORADIATION WITH INTENSITY MODULATED RADIATION THERAPY

While the increased therapeutic ratio achieved from the more accurate target delineation and beam shaping ability of 3DCRT was profound, there was still an excess of normal tissue being treated to relatively high doses (Figure 1A). A new method of treatment planning recommend by Brahme[65], and soon adopted by other investigators[66-68], approached radiation dose delivery by modulating the intensity of individual radiation beams to conform more closely to the target, thus avoiding treating excess normal tissue (Figure 1B). This new form of radiation, termed intensity modulated radiation therapy (IMRT), was shown to cause less toxicity when compared to 3DCRT in an early trial of prostate cancer patients[69]. The combination of taxanes combined with IMRT was first explored by Perrotti *et al*[70] in a phase Ⅰ/Ⅱ trial of weekly docetaxel (20 mg/m^2) and concurrent IMRT (72 Gy). Seventeen of twenty men with cT3, Gleason score ≥ 8, or Gleason score 7 with PSA > 10 ng/dL prostate cancer completed the treatment course without interruption. No significant hematologic toxicities(grades 2-4) were encountered among the 20 patients. Three patients had grade 3 toxicity (2 with dehydration, 1 with dyspnea) and no patients experienced grade 4 or 5 acute toxicity. At a short median follow-up of 11.7 mo, 15% of the treated patients experienced relapsed disease with no patient deaths.

The advent and widespread utilization of IMRT for

Table 1 Comparison of trials investigating chemoradiation for high-risk prostate cancer

Institution/group	*n*	Radiation technique	Comp Rx	GI toxicity	GU toxicity	Other toxicity
Continuous infusion 5-fluorouracil						
SWOG[29]	30	Whole pelvis if not surgically negative to 45 Gy + 70.2 Gy 3DCRT to prostate	97%	Gr 3: 7% Gr 4: 3%	Gr 3: 3% Gr 4: 3%	Multiple Gr 3: 13% (cumulative)
Daily estramustine phosphate + weekly vincristine						
Henry Ford Hospital[36]	65	4-field pelvis to 45 Gy + 65-70 Gy 3DCRT to prostate	71%	Gr 3: 0% Gr 4: 2%	Gr 3: 0% Gr 4: 0%	Leukopenia Gr 3: 2%
MSKCC[37]	27	3DCRT to prostate and SV	85%	Gr 3: 35% Gr 4: 0%	Gr 3: 48% Gr 4: 11%	Hematologic Gr 3: 8% Liver Gr 3: 7%
Daily estramustine phosphate						
Wayne State[39]	18	Prostate and SV to 50.4-70.2 Gy *via* 4-field + 3DCRT to prostate 70.2 Gy	78%	Not reported	Not reported	Leukopenia Gr 3: 12% Venous thrombosis Gr: 6% MI Gr 4: 6%
Weekly docetaxel						
UMDNJ[52]	22	3DCRT to prostate to 70.2 Gy	100%	Gr 3: 9% Gr 4: 0%	Gr 3: 0% Gr 4: 0%	No Gr 3 or 4
Europe[53]	50	4-field pelvis to 46 Gy + 70 Gy to prostate and proximal SV *via* 3DCRT or IMRT	92%	Gr 3: 6% Gr 4: 2%	Gr 3: 4% Gr 4: 0%	MI Gr 4: 2%
St. Peter's[70]	20	72 Gy delivered *via* IMRT (no further details)	85%	Gr 3: 0% Gr 4: 0%	Gr 3: 0% Gr 4: 0%	Dypsnea Gr 3: 5% Dehydration Gr 3: 10%
UNC[72]	18	Prostate and proximal SV 78 Gy with IMRT	89%	Gr 3: 11% Gr 4: 0%	Gr 3: 0% Gr 4: 0%	Leukopenia Gr 3: 28% Liver Gr 3: 6%
Medical University of South Carolina[73]	19	Prostate and proximal SV 45 Gy + 77.4 Gy prostate with IMRT	89%	Gr 3: 11% Gr 4: 0%	Gr 3: 0% Gr 4: 0%	Fatigue Gr 3: 11%
Biweekly Paclitaxel						
NYU[64]	22	4-field pelvis to 39.6 Gy + 63-73.8 Gy to prostate and proximal SV *via* 3DCRT	100%	Gr 3: 18% Gr 4: 0%	Gr 3: 0% Gr 4: 0%	No Gr 3 or 4

Comp Rx: Percentage of patients completing all protocol treatment; GI: Gastrointestinal; GU: Genitourinary; Gr: Grade; SV: Seminal vesicles; MI: Myocardial infarction; SWOG: Southwest Oncology Group; MSKCC: Memorial Sloan Kettering Cancer Center; UMDNJ: University of Medicine and Dentistry of New Jersey; UNC: University of North Carolina; NYU: New York University; 3DCRT: Three dimensional conformal radiation therapy; IMRT: Intensity modulated radiation therapy.

prostate cancer has led to radiation oncologists routinely treating patients to doses of 78 Gy or greater[71]. Combining high-dose IMRT with chemotherapy for prostate cancer was first published by Chen *et al*[72] in 2012 in a phase I docetaxel dose escalation feasibility study. Eighteen patients with node-negative prostate cancer and cT3-4, Gleason score ≥ 8, or PSA ≥ 20 ng/dL disease characteristics were treated with 24 mo of leuprolide started 3 mo before the chemoradiotherapy consisting of 78 Gy delivered *via* IMRT and escalating dose levels of weekly docetaxel (10, 15, and 20 mg/m^2). Grade 3 diarrhea occurred at each of the first two docetaxel dose levels but upon cohort expansion no further grade 3 toxicity was seen. There were no grade 4 or 5 toxicities reported leading the authors to conclude that docetaxel given weekly at 20 mg/m^2 appears safe. At a median follow-up of 26 mo biochemical progress-free survival was 94%.

From 2006-2010, another phase I docetaxel dose escalation study was performed with docetaxel doses higher (up to 30 mg/m^2) than those investigated in the aforementioned studies[73]. Nineteen patients with node-negative prostate cancer and cT2c-4, pretreatment PSA level ≥ 20, or Gleason score ≥ 8 disease characteristics were treated with combined androgen blockade for 4 mo starting 2 mo before the start of chemoradiation as well as treatment with a gonadotropin-releasing hormone (GnRH) analog alone for 24 mo after the completion of chemoradiation. Patients were treated with IMRT to 77.4 Gy with escalating weekly docetaxel in planned cohorts of 3 patients (10-30 mg/m^2). No grade 3 toxicities were seen in any of the patients treated up to a docetaxel dose of 25 mg/m^2. One patient of the three that were treated with docetaxel at 30 mg/m^2 experienced grade 3 dose-limiting diarrhea and this was determined to be the MTD of weekly docetaxel. At a median follow-up of 41 mo all patients achieved a PSA nadir of < 1 ng/dL, including 13 patients who had an undetectable PSA level with a biochemical progression-free survival of 78.9% in the entire cohort.

CONCLUSION

The studies discussed and summarized in Table 1

provide evidence supporting the safety and preliminary efficacy of a combined chemoradiation approach in men with high-risk prostate cancer; a disease with a historically poor cure rate. Current technology has allowed for radiation dose escalation and higher doses of chemotherapy to given with even less toxicity. These results, while promising, are only useful if randomized, phase III trials are undertaken to prove the utility of chemoradiation over androgen depravation and radiation alone. Chemoradiation could even be investigated in an intermediate-risk population in men who wish to avoid ADT. For this to be proven safe, randomized trials examining efficacy and carefully measured patient reported outcomes need to be conducted.

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