Role of radiation therapy in locally advance prostate cancer

:by

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- Radiotherapy given by external beam or brachytherapy techniques is a second treatment option for men withclinically localized prostate cancers. With the availability of sophisticated treatment planning systems and imageguided approaches, there have been significant advances in radiotherapy enabling higher doses to be delivered more safely, and concomitant improvements in disease-free survival outcomes.
- Intensity-modulated externalbeam radiotherapy (IMRT) has become a standard mode of treatment delivery and has facilitated the application of higher radiation dose levels of ≥80 Gy, with lower risks of late rectal and urinary toxicities.
- Such treatments coupled with image guidance have enabled the routine use of tighter margins, incorporating less normal tissue within the high-dose region and leading to further decrements in late toxicities.
- Brachytherapy using permanent (low-dose-rate [LDR]) or temporary radioactive implants (high-dose-rate [HDR]) within the prostate alone or combined with IMRT is another commonly used radiotherapeutic approach.
- This approach has also improved with more accurate image guidance and intraoperative real-time planning for brachytherapy, resulting in more highly conformal dose distributions, which in turn has resulted in better outcomes and lower toxicity rates, relative to what has been previously reported. In some cases,

IMRT reduced the risk of gastrointestinal toxicities and rates of salvage therapy compared to 3D?CRT in some but not all older retrospective and population-based studies,although treatment cost is increased.

- ADT is used in several contexts: to improve local eradication of locally advanced tumors by reducing tumor size, to eliminate tumor clonogens inherently resistant to radiotherapy by impairing DNA repair pathways, and/or to reduce prostate volumes by 30% to 40%, which improves the ability to deliver maximal radiation dose levels without exceeding the tolerance for the surrounding normal tissue.
- Hormone therapy also has a favorable effect on micrometastatic disease that may be present at the time of diagnosis in men with high-risk tumors.

- There are several criteria used to help select the most appropriate radiotherapeutic intervention for the patient with localized disease.
- For patients with low-risk disease in whom AS may not be considered—owing to PSA velocity, the presence of a dominant lesion on imaging studies, or a larger volume of disease determined by biopsy—EBRT as monotherapy or brachytherapy alone are excellent treatment options.

- Larger prostate volumes, the presence of urinary obstructive symptoms, and medical comorbidities may influence the selection away from a brachytherapy-based treatment.
- In contrast, brachytherapy may be the preferred choice for patients without these factors because of its excellent ablative capabilities (leading to longterm PSA relapse-free survival [RFS] outcomes) and its convenience (as a treatment accomplished in a single outpatient setting).
- For patients with intermediate- and higher risk disease, combined modality treatments including brachytherapy and supplemental IMRT are preferred to allow for the delivery of a high and concentrated dose of radiation to the prostate.
- In fact, in a recently published randomized trial, significant improvements in the long-term biochemical RFS outcomes were demonstrated among patients who were treated with combined brachytherapy and supplemental EBRT compared to high-dose conformal EBRT alone.

- Moderate hypofractionated EBRT regimens are becoming more frequently used due to the emergence of favorable results of phase III trials and represent another therapeutic option for patients with localized disease(2.4-4gy/f).
- Toxicity was similar between moderately hypofractionated and conventional regimens in some but not all of the trials
- Ultrahypofractionated EBRT regimens delivered via stereotactic body radiation therapy have generated increasing interest; however, although the early results are excellent and appear comparable to the best results achieved with IMRT, the long-term results of this approach are not yet available, and results of ongoing trials are awaiting more mature follow-up
- An ASTRO/ASCO/AUA evidence-based guideline regarding the use of hypofractionated radiation in men with localized prostate cancer concluded that moderatelyfractionated regimens are justified for routine use in this setting and provides more detail on the topic

Role of Dose Escalation in Patients with Clinically Localized Disease

- studies have generally demonstrated a 10% to 20% improvement in 5- to 10-year PSA survival outcomes, respectively, when higher doses of 78 to 80 Gy are applied, compared with dose levels of 70 Gy, and such benefits have been observed for low-, intermediate-, and high-risk cohorts.
- Although OS benefits have not been demonstrated with dose escalation, improvements in distant metastases–free survival are emerging with longer follow-up, suggesting that survival benefits will be seen as these studies mature.
- In one report, a reduction in death due to prostate cancer was noted at 10 years for intermediate- and high-risk patients treated with doses of 78 Gy, compared with those treated at 70 Gy.

- Daily prostate localization using image-guided RT (IGRT) is essential with either 3D-CRT or IMRT for target margin reduction and treatment accuracy.

Imaging techniques, such as ultrasound, implanted fiducials,

- electromagnetic targeting and tracking, or endorectal balloon, can improve cure rates and decrease complication

Data suggested that EBRT and radical prostatectomy were effective for the treatment of localized prostate cancer.

- EBRT of the primary prostatecancer shows several distinct advantages over radical prostatectomy.
- EBRT avoids complications associated with operation, such as bleeding and transfusion-related effects, and risks associated with anesthesia, such as myocardial infarction and pulmonary embolus.
- 3D-CRT and IMRT techniques are widely available and are possible for patients over a wide range of ages.
- EBRT has a low risk of urinary incontinence and stricture

and a good chance of short-term preservation of erectile function.

- that the most effective form of dose intensification is achieved when EBRT is combined with brachytherapy.
- In such cases, the biologic dose is enhanced with the combined treatments leading to a greater ablative effect on the prostatic epithelium

- A retrospective comparison from MSKCC demonstrated improved long-term PSA RFS outcomes and a reduction in the incidence of distant metastases among intermediate-risk patients treated with brachytherapy combined with IMRT compared to high-dose IMRT alone
- The NCCN Guidelines Panel consensus was that modern EBRT and surgical series show similar progression-free survival in patients with low-risk disease treated with radical prostatectomy or EBRT

Technical Aspects of Prostate Brachytherapy.

- Transperineal ultrasound-guided approach
- The two most commonly used radioisotopes for permanent seed brachytherapy are iodine-125 (125I) and palladium-103 (103Pd).
- The half-life of 125I is 60 days, with a mean photon energy of 27 KeV and an initial dose rate of 0.07 Gy per hour.
- In contrast, the half-life of 103Pd is 17 days, with a mean photon energy of 21 KeV and an initial dose rate of 0.19 cG per hour. The active periods for 125I and 103Pd are 10 and 3 months, respectively.
- When 125I is used, the typical prescription dose is 144 Gy; 125 Gy is routinely used for 103Pd

Combined Brachytherapy and External-Beam Radiotherapy

- Combined brachytherapy and EBRT is considered to be a more suitable treatment option than implantation alone for patients with unfavorable intermediate- or high-risk disease.
- The combined approach effectively delivers an increased dose of radiation that has been estimated to have a biologic equivalent that well exceeds a 100-Gy dose of EBRT.
- Conventional or conformal-based techniques are used to deliver 45 to 50 Gy of EBRT to the prostate
and periprostatic tissues.
- If an LDR boost is used, the brachytherapy prescription dose is 90 to 100 Gy for 103Pd implants and 110 Gy for 125I implants.
- In the absence of clinical trials comparing HDR brachytherapy boosts with LDR boosts or establishing the optimal sequence of therapy (brachytherapy boost preceding EBRT or vice versa) or the preferred isotope to be used for combined-modality therapy, there is no definitive evidence demonstrating the superiority of a particular treatment strategy over another.

- HDR brachytherapy offers several potential advantages over other techniques.
- Taking advantage of anafterloading approach, the radiation oncologist and physicist can more easily optimize the delivery of radiotherapy to the prostate, reducing the potential for underdosage (“cold spots”).
- This technique also reduces radiation exposure to the radiation oncologist and others involved in the procedure, compared with that from permanent interstitial implantation.
- Finally, HDR brachytherapy boosts may be radiobiologically more efficacious in terms of tumor cell kill for patients with increased tumor bulk or adverse prognostic features, compared with LDR boosts using 125I or 103Pd

Adjuvant Radiation Therapy for High-Risk Patients After Radical Prostatectomy

- (SWOG) trial 8794 :
- 425 patients with high-risk localized disease who were randomized to receive either 60 to 64 Gy to the prostatic fossa or only observation, have demonstrated a survival benefit of adjuvant radiotherapy in high-risk patients after RP. The 10-year distant metastases–free survival and OS rates were 71% and 74% for the adjuvant radiotherapy arm, compared with 61% and 66% for the observation arm
- EORTC 22911 :
- 1,005 patients with positive surgical margins or pT3 (ECE and SVI) disease; these patients were randomized to receive either adjuvant EBRT (50 Gy to the prostatic fossa and periprostatic tissue plus a 10- to 14-Gy boost to the prostatic fossa only) or no immediate treatment.187 A published update of this study (median follow-up, 10.6 years) showed that adjuvant radiotherapy improved the biochemical PFS rate from 40.1% to 60.6% ($P < .0001$); the 10-year rate of locoregional relapse was 7.3% for the adjuvant radiotherapy group and 16.6% for the control group. There was no difference in prostate cancer mortality (HR, 0.78; $P = .34$): 10-year prostate cancer mortality was 3.9% for the adjuvant irradiation group versus 5.4% for the observation group

- phase III trial from Germany (ARO 96-02):
- randomized 388 patients with pathologic T3 prostate cancer with undetectable postoperative PSA levels to receive either adjuvant radiotherapy or observation. The 10-year PFS was 56% for the adjuvant radiotherapy group and 35% for the observation group ($P < .0001$) with no survival benefit

EBRT to the Primary Tumor in Low-Volume M1 Disease

- Patients with newly diagnosed, low-volume metastatic prostate cancer can be considered for ADT with EBRT to the primary tumor based on results from the randomized controlled phase 3 STAMPEDE trial

In this multicenter, international study, 2061 patients were randomized to life long ADT with or without EBRT to the primary tumor (either 55 Gy in 20 daily fractions over 4 weeks or 36 Gy in 6 weekly fractions over 6 weeks).

- The primary outcome of OS by intention-to-treat analysis was not met (HR, 0.92; 95% CI, 0.80–1.06; P = .266), but EBRT improved the secondary outcome of failure-free survival EBRT improved OS (adjusted HR, 0.68; 95% CI, 0.52–0.90), prostate cancer-specific survival (adjusted HR, 0.65; 95% CI, 0.47–0.90), FFS (adjusted HR, 0.59; 95% CI, 0.49–0.72), and progression-free survival (adjusted HR, 0.78; 95% CI, 0.63–0.98) in patients with low metastatic burden, but not in patients with high metastatic burden

- The panel recommends against EBRT to the primary tumor in the case of high-volume M1 disease based on the HORRAD and STAMPEDE trials.

  No improvement in OS was seen from the addition of EBRT to the primary when combined with standard systemic therapy in patients with high-volume M1 disease in either trial.

Radiation for Distant Metastases

Recent studies have confirmed the common practice in Canada and Europe of managing prostate cancer with bone metastases with a short course of radiation.
A short course of 8 Gy x 1 is as effective as, and less costly than, 30 Gy in 10 fractions.
In a randomized trial of 898 patients with bone metastases, grade 2–4 acute toxicity was observed less often in the 8-Gy arm (10%) than the 30-Gy arm (17%) (P = .002); however, the retreatment rate was higher in the 8-Gy group (18%) than in the 30-Gy group (9%) (P < .001).
In another study of 425 patients with painful bone metastases, a single dose of 8 Gy was non-inferior to 20 Gy in multiple fractions in terms of overall pain response to treatment.
Most patients should be managed with a single fraction of 8 Gy for non-vertebral metastases based on therapeutic guidelines from the American College of Radiology

THANK YOU