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INVITED OPINION

Prostate Cancer

Optimal management of prostate cancer with lethal biology – state-of-the-art local therapy

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Defining prostate cancer with lethal biology based upon clinical criteria is challenging. Locally advanced/High-Grade prostate cancer can be downstaged or even downgraded with cure in up to 60% of patients with primary therapy.[1–5] However, what is known is that high-grade prostate cancers have a greater potential for recurrence and progression to metastatic disease, which can ultimately result in a patient's death. Patients with clinical features of "high-risk" prostate cancer (cT2c, PSA >20, ≥ Gl 8 on biopsy) are more likely to harbor more aggressive pathologic findings. The optimal management of high-risk prostate cancer is not known as there are not prospective studies comparing surgery to radiation therapy (RT). Retrospective and population-based studies are subject to many biases and attempts to compare surgery and radiation have demonstrated mixed results. Some show equivalent survival outcomes[6] while others showing an advantage of surgery over RT.[7–11] Local therapy for high-risk disease does appear to be beneficial. Improved outcomes realized with local therapy have been clearly demonstrated by several prospective studies evaluating androgen deprivation therapy (ADT) alone versus ADT plus RT. The combination of local with systemic treatment showed improved disease-specific and overall survival outcomes.[12–14] Unfortunately, primary ADT for N0M0 prostate cancer is still inappropriately applied in general practice.[11] While the surgical literature is largely retrospective, it too demonstrates that surgery in the setting of high-risk prostate cancer is effective in providing durable disease-specific and overall survivals.[2,3,15]

Whether both treatment modalities provide equivalent results is yet to be determined. In fact, many patients may benefit from a multimodality approach potentially including surgical excision, followed by postoperative radiation with or without ADT. However; when initiating therapeutic strategies, there may be certain clinical scenarios where relevant clinical findings or patient history could direct a clinician toward an optimal therapy. These decisions are typically based on inherent risks, theoretical concerns or the preponderance of evidence surrounding a single aspect of the particular clinical scenario. The following are clinical scenarios where RT or surgery may be considered as the best initial treatment for primary therapy in cTxN0M0 prostate adenocarcinoma. While this is by no means meant to be a strict guide for application of therapy, it does call to attention considerations as to appropriate clinical decision-making.

SURGERY IS BEST

Accepted circumstances

Prior pelvic radiation

Radiation has demonstrated effects on prostate adenocarcinoma but also has effects on adjacent in-field benign tissue. There are ample data on the maximum tolerated doses of radiation that can be applied to specific tissues and organs. Radiation oncologists use the quantitative analysis of normal tissue effects in the clinic (QUANTEC) to provide parameters on acceptable exposure of normal tissues.[16] This is based on demonstrated clinical toxicities seen with escalating radiation exposure. Prior radiation exposure to the pelvis becomes clinically relevant in patients with a prior history of RT for the treatment of seminoma, pelvic sarcoma or rectal carcinoma. It may also become important after prior pelvic surgery resulting in shifting small bowel proximity, preventing adequate dose administration to the prostate. There is also no consensus as to the whether time lapse from prior RT exposure limits toxicity. Longer intervals between therapies may make overlapping fields less relevant, but there is no consensus on an appropriate interval where prior exposure would no longer influence treatment decisions. Clinicians use their best judgment in these clinical scenarios, but it would seem surgical resection may provide a superior treatment option over primary RT if a patient has a history of prior pelvic RT or pelvic surgery.

Inflammatory bowel disease

Patients with a history of inflammatory bowel disease (IBD-ulcerative colitis or Crohn's disease) may be at greater risk of acute and late complications or toxicity with radiation exposure. In a study by Willet *et al*. evaluating acute and late toxicities of patients with IBD undergoing radiation for abdominal pelvic neoplasms, a substantial portion of patients, had severe acute toxicity (21%) and toxicity necessitating later hospitalization or surgical repair (29%), resulting in 46% of patients having some form of severe toxicity.[17] These findings would suggest that RT in the setting of IBD leads to unacceptable toxicity and should be avoided or used with extreme caution. Interstitial brachytherapy as an alternative radiation option has mixed results in the treatment of prostate cancer in IBD patients. There are conflicting retrospective studies showing Grade 3 acute and late toxicities of 15%–23%,[18] while another study showed Grade 3 toxicity was nonexistent (0%) in patients with medically

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controlled IBD.[19] In standard practice, single modality brachytherapy is traditionally reserved for low-risk (nonlethal) prostate cancer patients, while high-risk PCa patients with lethal biology would more commonly be treated with combination brachytherapy with external RT boost in addition to long-term androgen suppression (LTAS). The reported outcomes of IBD patients with any external RT component would suggest that RT be avoided as the primary treatment for lethal prostate cancer in patients with IBD.

COMMON CLINICAL CONDITIONS

Lower urinary tract symptoms

A common clinical consideration in the treatment of prostate cancer is the patient's presenting urinary status. Patients lower urinary tract symptomatology is often measured with the American urologic association symptom index (AUA-SI) or using EPIC questionnaires.[20,21] This information along with visual findings and volume estimates from transrectal ultrasonography, magnetic resonance imaging, cystoscopy and when indicated urodynamic testing, has provided data to predict posttreatment outcomes. There is evidence that patients experience greater genitourinary toxicity after radiation therapy when the prostate size is >40 g.[22–24] While others have demonstrated that radical prostatectomy results in improved AUA-SI postoperative and that this improvement is durable 48 months after surgery.[25] In the ProstQA study, patients with obstructive symptoms were found to have resolution of symptoms after RP 65% of the time.[26–28] These studies would suggest that obstructive symptoms warrant emphasis when counseling patients on treatment options. Surgical resection may be a more appropriate treatment option for men with significant urinary symptoms, particularly in men with large median lobes or in men where the prostate is felt to be contributing to the outlet obstruction generating the symptoms.

High-risk and long-term androgen suppression (LTAS)

Perhaps a more controversial scenario is the high-risk prostate cancer patient with a disease that has significant lethal potential and selecting the most appropriate initial therapy. Several retrospective studies have demonstrated improved cancer-specific mortality with RP over RT.[7–9,11] These largely observational studies that lack randomization have significant confounding factors, in addition to inherent unknown confounders. These limitations raise too many questions as to the validity of the conclusions that patients undergoing RP have improved outcomes in comparison to RT for high-risk disease. In addition, studies also exist that demonstrate equivalent cancer-specific survivals for RP (92% CSS) versus EBRT in combination with ADT (92% CSS).[6] What is clear from prospective studies evaluating RT and ADT is that LTAS in combination with RT results in improved outcomes compared to RT alone or RT with short-term androgen suppression (STAS).[29–31] These findings have led to the guideline recommendations by the AUA, EAU and NCCN for 2–3 years of ADT in combination with RT for high-risk prostate cancer.[32–34]

LTAS may have significant effects on an individual's quality of life. Potential side effects include fatigue, hot flashes, decreased libido and erectile dysfunction, in addition to potential long-term consequences with resultant coronary disease, diabetes, lipid dysfunction, and anemia.[35–39] Given surgical resection has been shown to have at least equivalent if not improved cancer-specific outcomes to RT/ADT combination therapy, it is reasonable to consider surgery as the initial step in the treatment of high-risk disease. This may help to limit the side effects of LTAS and allow for sequential therapies with the least additive toxicity. Postoperative RT can be beneficial with limited toxicity,[40–42] while salvage radical prostatectomy for radioresistant disease has substantial surgical risks and results in poor functional outcomes.[43–45] This may be most relevant when considering the younger prostate cancer patient who is likely to have the greatest need for subsequent therapies given the long life expectancy. Upfront RP could preclude the need for early exposure to ADT and may also avoid the risk of secondary malignancies from RT, which seems to increase with longer intervals from radiation exposure (HR 1.39 [CI: 1.29–1.50] at 5–9 years and 1.91 [CI: 1.53–2.38] at ≥15 years).[46]

Another potential limitation of RT in the setting of high-risk disease is based on limitations of clinical staging. Patients classified as intermediate risk based on clinical parameters would routinely receive RT with short-term androgen suppression (STAS). However, there is a risk that the patient could be understaged, risk of being upgraded on pathology or even having occult node positive disease with a reported rate of up to 30% in some high-risk series.[3,15,47] These men would be vastly undertreated with RT and STAS. Identification of risk factors for postoperative reclassification to a high-risk category could potentially identify men who would benefit from RP or at minimum RT in combination with LTAS. In our clinical practice, discordant findings such as a mismatch digital rectal exam, PSA or tumor volume (number of cores, volume per core) lend to more substantial local staging evaluations with MRI imaging and often repeat directed biopsies (fusion or MRI guided) in order to identify sites of more aggressive disease. While rebiopsy may be necessary for RT treatment planning, additional biopsies are often unnecessary when RP is the planned initial treatment as the results typically do not alter the treatment plan.

SPECIAL CONSIDERATIONS

Variant histology

There has been a significant interest in variant histologic patterns in prostate adenocarcinoma. While neuroendocrine or small cell differentiation lend themselves to chemotherapeutic interventions, there are other histologic patterns that alter local therapeutic options as well.[48] Pathologists have more commonly been identifying ductal prostate adenocarcinoma, which was thought to be a rarer variant of prostate cancer. This seems to be found in 0.13%–6% of prostate cancers, is often associated with high Gleason scores, advanced stage, often presents with obstructive symptoms and its presence is associated with a higher cancer-specific mortality.[49] When evaluating the effects of therapy, authors at MD Anderson Cancer Center found that local recurrences were found in 56% of patients receiving primary RT, but only 17% of patients with RP. In addition, patients with pure ductal adenocarcinomas may have better outcomes than patients with mixed ductal and pure adenocarcinoma.[50] Given the high-risk for recurrence and potential radioresistance of the ductal variant local control with surgical resection may be the preferred treatment in men considered as appropriate surgical candidates. Optimal treatment for more rare variants such as sarcomatoid is unclear at this time as they tend to present in later stages and are often considered unresectable at presentation.[51]

Genetic mutations

As research into the genetics behind malignancies have become more understood, and there is clear evidence that specific mutations are associated with cancer diagnoses, considerations must be made as to optimal therapeutic approaches for cancer treatment. Two mutations present in prostate cancer patients that have raised concern over the use of RT in the treatment of prostate cancer are mutations in p53 (Li-fraumeni syndrome) and BRCA1/2. p53 is a tumor suppressor

and mutations can lead to unregulated cell growth and tumor formation.[52] BRCA1/2 genes are involved with genome stability and assist in DNA repair.[53] Mutations in both have been associated with prostate cancer in men. With breast cancer being the most prevalent cancer diagnosis in women in the U.S., there are increasing numbers of patients being diagnosed with BRCA1/BRCA2 mutations as a result. This may have significant implications for prostate cancer screening in men with immediate family members being diagnosed with these mutations potentially finding themselves at greater risk of prostate cancer. However, this also may affect treatments offered due to the risks of upgrading/staging and appropriateness for placement on active surveillance.[54] Currently, there is limited knowledge of the long-term effects of radiation exposure in patients with these germline mutations. The preponderance of evidence would suggest that RT may cause the exposed tissues to be at a greater risk of secondary malignancies. While we know RT exposure increase the risk of secondary malignancies based on population-based studies,[46] it may be that patients with germline mutations are at even greater risk. While malignancy is at the forefront of concerns, there is also the theoretical potential for an increased risk of toxicity due to normal tissue exposure to RT. If true, this could lead to increased side effects related to bladder, bowel, continence and sexual function. Until, we have a better grasp of the effects of RT on patients with germline mutations surgical therapy is potentially the safer alternative in the treatment of high-risk prostate cancer.

CONCLUSION

Optimal management of prostate cancer would provide oncologic efficacy while minimizing side effects and long-term sequelae. Increasing understanding of the risks and benefits attributed to specific prostate cancer treatments allows the clinician to assimilate the data and generate an optimal treatment plan for an individual patient. Involvement of several providers in a multi-disciplinary environment allows for open communication and collaboration between radiation oncologists, urologic oncologists and medical oncologists when developing these treatment plans. A thorough understanding of treatment options in addition to the basic elements of an individual's medical history and genetic background can allow for selecting the most appropriate application of specific therapies based on patient-specific factors/circumstances.

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

When patients have localized prostate cancer with clear lethal biology, then the active surveillance option is deemphasized to patients with major morbidity issues, and the focus turns to surgery versus radiation comparisons. While much is published on the key outcomes of surgery in terms of oncologic results and functional recovery, a less emphasized area are specific conditions where surgery can be strongly recommended, rather than presented as an "option." In his focused review, Chapin identifies several such conditions ranging from prior pelvic radiation, inflammatory bowel disease, and lower urinary tract symptoms. For other patients, the lack of hormonal therapy required for most surgical patients can be considered. These are mostly arguments rather than guidelines statements, but the evidence is detailed. At my home center, the majority of prostate cancer patients are seen in a multidisciplinary setting with a nurse practitioner, surgeon, and radiation oncologist. The criteria for active surveillance are established and agreed. Candidates for the treatment are then counseled on options including clinical trials.[55] As the Madsen study illustrates, patients are given a letter summarizing these options, standard approaches, and available clinical trials (treatment, quality of life and/or laboratory). Unpublished data from this same cohort show a historic trend of 55% choosing surgery, 30% choosing radiation therapy, 10% active surveillance, and 5% alternatives. There are certainly age-related trends, and more modern cohorts are increasing in surveillance selection.

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