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Review Article

The 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 Published by Elsevier Inc. on behalf of American Brachytherapy Society.

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

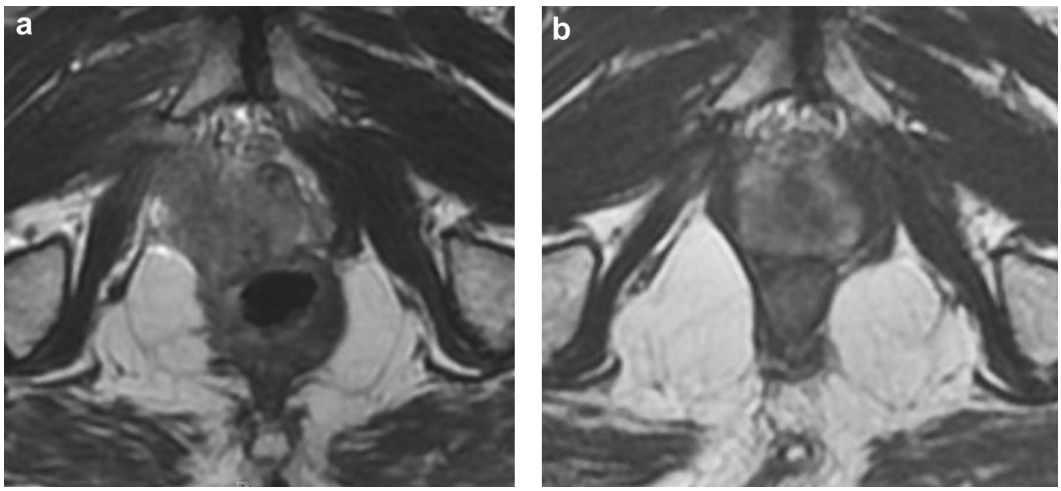

Fig. 1. T2 weighted axial MRI images at the level of the prostate apex demonstrating local effect of ADT. (a) Image taken prior to ADT. (b) Image taken post ADT.