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RESEARCH HIGHLIGHT

The importance of combined radiation and endocrine therapy in locally advanced prostate cancer

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The management of all stages of prostate cancer has become an increasingly complex task as new treatment paradigms are tested and the results of large randomized studies become available. Despite these advances, prostate cancer remains the second leading cause of cancer death and the seventh overall cause of death in men in the United States.[1] The advent of prostate-specific antigen (PSA) testing in the 1980s resulted in a significant downward stage migration such that many men now present with the earliest and most curable form of the disease.[2,3] Despite this fact, high-risk locally advanced prostate cancer remains a common and complex problem facing clinicians across the world.

While many studies have focused on patients with locally advanced prostate cancer, there is little consensus on what specific clinical and pathological features are required for this diagnosis. Indeed, when 155 oncologists and urologists in the United Kingdom were asked to define the term, they provided 95 different answers.[4] In the United States, patients are generally grouped into low, intermediate or high-risk disease based on their risk of disease recurrence following therapy.[5] The use of PSA and Gleason score in these risk groups also predicts for those with occult extraprostatic extension not readily palpable by digital rectal exam.[6,7] As such, utilization of all of these factors likely provides better risk stratification than any one factor alone.

The confusion over the definition of locally advanced prostate cancer also extends to its management. External beam radiation therapy (EBRT) has been the historically preferred method of treatment due to the increased risk of incomplete resection with radical prostatectomy. The value of combining androgen deprivation therapy (ADT) with EBRT became clear in the 1990s with the publication of results from RTOG 8531 showing a clear benefit for adjuvant hormonal therapy for those with high Gleason score.[8] Those with bulky disease were also shown to benefit from combined modality therapy in RTOG 8610.[9] Later trials showed that longer courses of androgen suppression, on the order of 2–3 years, were superior to regimens lasting only a few months.[10,11] It has been hypothesized, however, that all of the benefit seen in these patient populations are derived from the ADT component rather than the radiotherapy component.

The NCIC/MRC trial, recently published by Warde *et al.* in *The Lancet*, has provided us with robust data to refute this hypothesis.[12] In their study, patients with locally advanced prostate cancer (defined as cT3/T4, those with localized disease and a PSA of >40 ng ml^{-1} or those with a PSA >20 ng ml^{-1} and a Gleason score of 8 or higher) were randomized to indefinite ADT using orchiectomy or a luteinizing hormone-releasing hormone (LHRH) agonist *vs.* ADT plus EBRT. With a median of 6 years of follow-up, they demonstrated that the addition of EBRT to ADT reduced prostate cancer-specific mortality by 10% and improved overall survival by 8% at 7 years. EBRT was generally well tolerated with mild-to-moderate effects on bowel and bladder function at early time points. Severe late effects were uncommon with no clear differences between the arms as measured by multiple quality of life instruments.

These data confirm the findings of the SPCG-7 study which also showed a clear benefit in overall survival for patients treated with a combination of EBRT and ADT.[13] There are several notable differences between the two trials, however, which should be considered in interpreting them. The NCIC/MRC trial included more advanced patients with higher PSA levels than the SPCG-7 trial. Furthermore, surgical staging was required in SPCG-7 for those with PSA levels of >11 ng ml^{-1} and patients found to have node-positive disease were excluded from the trial. In comparison, less than 5% of patients in the NCIC/MRC trial underwent nodal dissection.

The difference in the initial management of the pelvic lymph nodes between these trials also informed their respective approaches to the delivery of EBRT. In SPCG-7, no attempt was made to treat the pelvic nodes, while in NCIC/MRC, all patients received 45 Gy to the pelvis using a standard four-field box technique. The utility of treating the pelvic lymph nodes in those with high-risk prostate cancer remains a topic of significant controversy. This question was specifically addressed in RTOG 9413 in which patients with high-risk disease were randomized to receive whole pelvis or prostate only RT.[14] A progression free survival benefit was seen on first analysis for patients treated with whole pelvic radiation but this benefit disappeared at later time points. Furthermore, the timing of ADT in this trial limited the analysis of treating the whole pelvic volume.[15] As such, the value of whole-pelvic RT remains open to interpretation.

Another clear difference between the two aforementioned studies is the type of ADT prescribed. While the NCIC/MRC trial allowed orchiectomy or treatment with a LHRH agonist, SPCG-7 used LHRH agonist treatment for only 3 months after which time patients received peripheral androgen blockade with flutamide alone. Despite these differences in approach, the similar results of these trials suggest that either is justifiable and that both appear to combine well with EBRT. Both trials chose to prescribe ADT until progression

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rather than using the 2–3 years of courses commonly prescribed at many centers. To date, there has been no direct comparison of a multiyear approach and lifelong ADT. Despite this, the significant side effects of lifelong ADT such as bone demineralization and increased risk of diabetes make shorter courses somewhat more attractive.

Finally, the authors of the NCIC/MRC study demonstrate that the addition of EBRT to ADT is well tolerated with mild but time-limited differences in bowel and bladder toxicity. Similar results were seen in SPCG-7 when patient-reported quality of life was analyzed.[16] It is important to note, however, that both studies utilized three-dimensional conformal radiotherapy delivering doses between 65 and 70 Gy to the prostate. Intensity modulated radiotherapy appears to reduce toxicity in patients treated with and without hormonal therapy compared to three-dimensional conformal radiotherapy in several retrospective comparisons.[17,18] As such, even lower toxicity may be seen in patients treated with this approach.

In conclusion, there are now two well-designed and executed randomized controlled trials comparing ADT alone or in combination with EBRT in the treatment of patients with locally advanced prostate cancer. Both of these studies show clear benefits in progression free and overall survival for a combined modality approach. Previous studies have also demonstrated that radiotherapy alone is not sufficient treatment for this subgroup of patients. As such, the combined use of EBRT and ADT for patients with locally advanced prostate cancer should be the recognized standard of care throughout the world.

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