Surgery or radiation: what is the optimal management for locally advanced prostate cancer?

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Introduction: *To date, randomized trials comparing radiotherapy to surgery for adenocarcinoma of the prostate are few. Lacking, are randomized comparisons between treatment modalities for the patient with high-risk locally advanced disease. Hence, there is a need to determine which approach offers superior results in these patients who comprise a significant proportion of those dying of prostate cancer. In this short review we highlight key studies that may provide interim answers while awaiting definitive results from randomized studies.*

Material and methods: *A MEDLINE literature review was performed of studies evaluating current treatment modalities for high-risk (TNM stage >T2b, PSA>10, Gleason ≥8) prostate cancer. Publications from 1975 to present were searched using the keywords: prostate cancer, locally advanced prostate cancer, high-risk prostate cancer, prostatectomy, external beam radiation, brachytherapy, and PSA-doubling time.*

Results: *Comparisons of different treatment modalities are difficult due to many factors, from uncertainties in clinical staging to the questionable equivalence of PSA failure. However, the general consensus is that low dose rate brachytherapy monotherapy is not ideal for high-risk patients. There are several options for combination therapy which show moderately good survival results. Because of the lack of prospective randomized trials comparing these approaches, matched analyses with uniform patient treatment and pathological review may provide an interim answer.*

Conclusion: *The optimal management for patients with locally advanced prostate cancer is unclear. While randomized clinical trials will eventually shed light on this question, interim solutions may provide some answers in the short term.*

Key Words: locally advanced prostate cancer, brachytherapy, radical prostatectomy

Introduction

Despite downward stage migration, there are still a significant number of men presenting with locally advanced disease.[1] These patients are at greater risk for local recurrence after definitive therapy, and are more likely to harbor occult metastasis. In patients with organ-confined prostate cancer, both surgery and radiation provide excellent cancer control. However, after radical prostatectomy (RP) for stage T2c disease, only 46%-49% of patients have demonstrated biochemical progression-free survival at 10 and 7 years respectively.[2,3] Similar survival rates have been published for multimodality radiotherapy (RT) protocols with and without neoadjuvant hormonal ablation,[4,5] however randomized study designs and long-term follow up are lacking.

When primary definitive therapy for high-risk adenocarcinoma of the prostate is considered, comparisons between surgery and radiation are difficult. Discovery of newer pre- and post-treatment

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risk factors for early failure (making comparisons with legacy prognostic factors difficult), varied definitions of failure, and lack of large randomized trails contribute to this. Current approaches to the treatment of locally advanced prostate cancer are prostatectomy with and without neoadjuvant and adjuvant androgen ablation, external beam radiotherapy with and without brachytherapy boost or external beam radiotherapy with neoadjuvant and adjuvant androgen ablation. To date, only one randomized trial has been published comparing radical prostatectomy and radiation therapy in patients with locally advanced disease.[6]

Monotherapy versus combined modality treatments

Growing evidence from large randomized trials,[7,8] has demonstrated that combination therapy, as opposed to monotherapy provides superior survival in high risk patients. Studies have demonstrated biochemical free survival rates (bRFS) of 44%-64% at 7-10 years in patients with pretreatment characteristics such as clinical stage T2c, PSA >10 ng/ml, or Gleason score ≥8, when treated with RP monotherapy.[3,9,10] More favorable survival rates for RP patients with T2c disease have been cited,[11] but 60% of the patients in the study were treated with adjunctive hormonal ablation therapy.

Outcomes for patients with high-risk prostate cancer have been improved by advances in external beam radiotherapy (EBRT) such as three-dimensional conformal radiotherapy with dose escalation, and intensity modulated radiation therapy (IMRT). In a large randomized trail at MD Anderson, EBRT dose escalation from 70 Gy to 78 Gy in patients with pretreatment PSA >10 ng/ml produced improved survival results of 64% bRFS in the 78 Gy group compared to 46% bRFS in the 70 Gy group[12] at 6 years. Brachytherapy monotherapy is designed to treat intracapsular tumor, and is not inherently effective treatment for locally advanced disease. Indeed, one study revealed the relative risk of PSA failure in intermediate-risk patients (stage T2b or Gleason score of 7 or PSA level >10 and ≤20 ng/mL) and high-risk patients (stage T2c or PSA level >20 ng/mL or Gleason score ≥8) treated with implant alone compared with RP were 3.1 and 3.0, respectively.[13]

Both the use of neoadjuvant (NHT) and adjuvant hormonal therapy with RP have been studied in an attempt to prevent or delay the recurrence of prostate cancer in the high-risk patient. Randomized studies with 3-4 months of NHT prior to surgery in patients with clinically-localized (T2b) prostate cancer have demonstrated a decrease in positive margins, but no advantage in survival.[14,15] One study which specifically targeted patients with clinical stage T3 and T4 disease, determined the 5-year survival estimate after RP and 4 months of adjuvant hormonal therapy to be 90%.[16] NHT has also been used with EBRT in patients with T3 and T4 disease, or Gleason score 8-10, and has been shown to significantly improve survival in prospective randomized trials by the European Organization for Research and Treatment of Cancer (EORTC) and the Radiation Therapy Oncology Group (RTOG).[7,17] Questions remain regarding how the biologic effect of androgen deprivation improves outcome in this setting. For example, it is unclear whether androgen deprivation affects the prostate itself, improving local cure, or systemic disease, or both. A potential disadvantage of NHT and RP is that hormonal ablation therapy alters prostate pathology resulting in an un-interpretable Gleason score in the prostatectomy specimen. This would hamper postoperative risk stratification and need for additional treatment.

Combination brachytherapy and EBRT in the high-risk patient is an available option, but one that has not been widely studied. The study with the longest follow-up is a multi-institutional observational cohort study from Seattle, WA.[18] High-risk patients (T2b, PSA>10ng/ml, Gleason 8-10) were found to have a 48% bRFS at 10 years. Unlike this study where androgen deprivation was not used, we have used a multimodality approach combining brachytherapy, EBRT (90 Gy), and neoadjuvant/adjuvant hormonal ablation therapy. Our early results indicate a 24-month recurrence-free survival of 88% before "PSA bounce" correction, and 92% after bounce correction.[4] In conclusion, it would appear that perhaps combined modality radiotherapeutic treatments offer an advantage over single modality approaches. Furthermore, androgen ablation appears to offer advantages when applied in conjunction with radiotherapy.

Surgery versus radiotherapy treatments

Few published studies have presented direct comparisons between surgery and radiation for adenocarcinoma of the prostate, much less for prostate cancer that is of clinical stage greater than T2b. Furthermore, only one, by Akakura et al, is a randomized trial.[6] This randomized trial was designed to compare RP versus EBRT in patients with stage B2 and C prostate cancer. Hormonal ablation

was used in both groups before and after the primary therapy. The median follow up period was 58 months, and survival analysis revealed progression-free survival rates of 91% in the RP group versus 85% in the EBRT group. This study was limited by a small sample size, and the differences in survival analysis between the two groups were not shown to be statistically significant. A larger, retrospective, multi-institutional comparison of RP, EBRT, and brachytherapy has been published by D'Amico et al.[13] The study presented a large cohort, and patients were stratified into low, intermediate, or high-risk for post therapy PSA failure based on pre-therapy PSA level, biopsy Gleason score, and clinical stage. In the high-risk cohort (stage T2c, PSA >20ng/ml, or Gleason ≥8), brachytherapy patients exhibited higher rates of PSA recurrence than with RP, even in patients who received neoadjuvant hormone ablation in conjunction with brachytherapy. The addition of androgen deprivation to implant therapy did not improve PSA outcome in high-risk patients but resulted in a PSA outcome that was not statistically different compared with the results obtained using RP or RT in intermediate-risk patients (stage T2b or Gleason score of 7 or PSA level >10 and ≤20 ng/mL).

In a pilot experience at our institution comparing RP with BT or combination BT (EBRT + BT), groups displayed estimated bRFS of 72% for the RP group, 72% for the combination BT group and 25% for the BT monotherapy group at 4 years. This data suggests (as has been found by others) that brachytherapy monotherapy appears inferior to the other two approaches in the high-risk patient. Biochemical failure for those results was defined as PSA>0.20. All these patients had pathology review by one genitourinary pathologist. Interestingly, the EBRT + BT group displayed the highest pre-treatment risk parameters compared to the other two groups. Of note is the fact that patients treated with radiotherapy had 2-3 months of neoadjuvant androgen ablation followed by a similar duration of adjuvant treatment. In addition to the overall analysis, a matched (for grade, stage and PSA) cohort analysis was performed between RP and combination brachytherapy, and the bRFS at 4 years were 72% and 78% respectively.

Does PSA failure after surgery or radiation have equivalent significance with respect to survival?

PSA failure after definitive treatment may occur from either localized or metastatic foci of disease. In addition, tumors that persist after radiation may have a different biology than those that survive surgical removal. Conceivably, the cancer biology of local recurrences after surgery would be similar to the initial tumors while those after radiation may have been altered by the radiation to either a more indolent or aggressive form of the disease. Therefore, we sought to determine a surrogate approach that would provide a practical way to assess the clinical impact of the PSA failure after surgery or radiation.

To do this we reasoned that it may be useful to compare the PSA doubling times of patients which have biochemical failure following localized treatment for high-risk prostate cancer in the matched cohort study described above. This approach appears reasonable since estimates of disease-specific mortality rates can be made using PSA-doubling time[19] which would provide some clues as to whether "all PSA failures are created equal".

Using our pilot data on matched cohorts of high-risk patients treated with either RP or EBRT + BT, we have found that patients in the RP group displayed more rapid PSA-doubling times than patients treated with combination EBRT + BT suggesting the latter would have reduced disease specific mortality. This observation raises interesting questions regarding how radiation may impact prostate tumor characteristics and appears not to support the notion that prostate cancer recurrence following radiotherapy results in a more aggressive tumor phenotype.

Conclusion

In conclusion, there is currently no consensus on the best approach for treating prostate cancer patients with locally advanced disease. Clearly, more randomized trials comparing surgery and radiation for this patient cohort are needed. Until those results are known, retrospective matched analyses with uniform patient treatment and pathological review may give us interim answers. □

References

1. Noldus J, Graefen M, Haese A et al. Stage migration in clinically localized prostate cancer. *Eur Urol* 2000;38(1):74-78.
2. Cheng WS, Frydenberg M, Bergstralh EJ et al. Radical prostatectomy for pathologic stage C prostate cancer: influence of pathologic variables and adjuvant treatment on disease outcome. *Urology* 1993;42(3):283-291.
3. Catalona WJ, Smith DS. Cancer recurrence and survival rates after anatomic radical retropubic prostatectomy for prostate cancer: intermediate-term results. *J Urol* 1998;160(6 Pt 2):2428-2434.

4. Coblentz TR, Bissonette EA, Williams KR et al. Multimodality radiotherapy and androgen ablation in the treatment of clinically localized prostate cancer: early results in high risk patients. *Prostate Cancer Prostatic Dis* 2002;5(3):219-225.
5. Ragde H, Korb LJ, Elgamal AA et al. Modern prostate brachytherapy. Prostate specific antigen results in 219 patients with up to 12 years of observed follow-up. *Cancer* 2000;89(1):135-141.
6. Akakura K, Isaka S, Akimoto S et al. Long-term results of a randomized trial for the treatment of Stages B2 and C prostate cancer: radical prostatectomy versus external beam radiation therapy with a common endocrine therapy in both modalities. *Urology* 1999;54(2):313-318.
7. Bolla M, Gonzalez D, Warde P et al. Improved survival in patients with locally advanced prostate cancer treated with radiotherapy and goserelin. *N Engl J Med* 1997;337(5):295-300.
8. Laverdiere J, Gomez JL, Cusan L et al. Beneficial effect of combination hormonal therapy administered prior and following external beam radiation therapy in localized prostate cancer. *Int J Radiat Oncol Biol Phys* 1997;37(2):247-252.
9. Pound CR, Partin AW, Epstein JI et al. Prostate-specific antigen after anatomic radical retropubic prostatectomy. Patterns of recurrence and cancer control. *Urol Clin North Am* 1997;24(2):395-406.
10. Bosch RJ, Kurth KH, Schroeder FH. Surgical treatment of locally advanced (T3) prostatic carcinoma: early results. *J Urol* 1987;138(4):816-822.
11. Lerner SE, Blute ML, Zincke H. Extended experience with radical prostatectomy for clinical stage T3 prostate cancer: outcome and contemporary morbidity. *J Urol* 1995;154(4):1447-1452.
12. Pollack A, Zagars GK, Starkschall G et al. Prostate cancer radiation dose response: results of the M. D. Anderson phase III randomized trial. *Int J Radiat Oncol Biol Phys* 2002;53(5):1097-1105.
13. D'Amico AV, Whittington R, Malkowicz SB et al. Biochemical outcome after radical prostatectomy, external beam radiation therapy, or interstitial radiation therapy for clinically localized prostate cancer. *JAMA* 1998;280(11):969-974.
14. Gomella LG, Zeltser I, Valicenti RK. Use of neoadjuvant and adjuvant therapy to prevent or delay recurrence of prostate cancer in patients undergoing surgical treatment for prostate cancer. *Urology* 2003;62(Suppl 1):46-54.
15. Klotz LH, Goldenberg SL, Jewett MA et al. Long-term follow up of a randomized trial of 0 versus 3 months of neoadjuvant androgen ablation before radical prostatectomy. *J Urol* 2003;170(3):791-794.
16. Powell IJ, Tangen CM, Miller GJ et al. Neoadjuvant therapy before radical prostatectomy for clinical T3/T4 carcinoma of the prostate: 5-year followup, Phase II Southwest Oncology Group Study 9109. *J Urol* 2002;168(5):2016-2019.
17. Lawton CA, Winter K, Murray K et al. Updated results of the phase III Radiation Therapy Oncology Group (RTOG) trial 85-31 evaluating the potential benefit of androgen suppression following standard radiation therapy for unfavorable prognosis carcinoma of the prostate. *Int J Radiat Oncol Biol Phys* 2001;49(4):937-946.
18. Sylvester JE, Blasko JC, Grimm PD et al. Ten-year biochemical relapse-free survival after external beam radiation and brachytherapy for localized prostate cancer: the Seattle experience. *Int J Radiat Oncol Biol Phys* 2003;57(4):944-952.
19. D'Amico AV, Moul J, Carroll PR et al. Prostate specific antigen doubling time as a surrogate end point for prostate cancer specific mortality following radical prostatectomy or radiation therapy. *J Urol* 2004;172(5 Pt 2):S42-46;discussion S46-47.