The Central Role of Radiation in Prolonging Survival for High-Risk Prostate Cancer

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Abstract

Prostate cancer represents a leading cause of cancer mortality in men, second only to lung cancer. A significant proportion of men who are diagnosed with high-risk or locally advanced prostate cancer will ultimately succumb to the disease, which has a 10-year cause-specific mortality of 26% with conservative treatment. Several randomized controlled trials demonstrated that the addition of radiation therapy (RT) to long-term androgen-deprivation therapy (ADT) for locally advanced prostate cancer resulted in a substantial improvement in overall survival compared with ADT alone. Despite these findings, undertreatment of high-risk prostate cancer is a growing problem, with increasing use of ADT monotherapy over time, particularly in elderly patients. In this review, we present the evidence for combined ADT and RT in the treatment of high-risk prostate cancer, and discuss the role of pelvic nodal RT, as well as treatment of elderly patients and those who are found to have positive pelvic lymph nodes.

Key words: Prostate cancer, radiation, androgen-deprivation therapy, pelvic lymph nodes, elderly

Clinical Scenario

A 77-year-old man presents to his primary care physician for evaluation after a single episode of rectal bleeding, which is found to be related to his known history of hemorrhoids. At the time of examination, he is found to have a firm prostate with prominent bilateral nodularity. Due to suspicion for prostate cancer, a prostate-specific antigen (PSA) test is given, which returns at 16.2 ng/mL. He then undergoes transrectal ultrasound-guided biopsy and is found to have Gleason score 4 + 4 disease in 8 of 12 cores, with 30% to 80% involvement of each core. Staging reveals no evidence for skeletal metastasis, but shows a single enlarged right internal iliac lymph node. The patient has good urinary and sexual function, and is otherwise in excellent health. After obtaining his diagnosis of high-risk prostate cancer (cT2c, Gleason score 4+4, PSA 16.2), he consults a physician who recommends androgen-deprivation therapy (ADT) alone. He presents to you seeking a second opinion, with questions regarding the necessity of radiation therapy (RT).

Introduction

Recent guidelines from the US Preventive Services Task Force recommend against routine PSA screening for the general population,[1] with the observation that approximately 1000 men need to be screened to prevent 1 death from prostate cancer. The authors comment that "most cases of prostate cancer have a good prognosis even without treatment."[1] This sentiment is reflected in increasing discussion on the overtreatment of low-risk prostate cancer[2] and the role of active surveillance.[3]

However, caution is warranted in categorizing prostate cancer as a "good cancer," as it represents a leading cause of cancer mortality in men, second only to lung cancer.[4] The majority of men diagnosed with locally advanced or high-risk prostate cancer will succumb to their disease within 15 years with conservative treatment.[5] In the example provided, given that an average 77-year-old male has a remaining life expectancy of approximately 10 years, it is noteworthy that the estimated 10-year cause-specific mortality from conservatively treated high-risk prostate cancer is approximately 26%.[6] Treatment of locally advanced and high-risk prostate cancer, therefore, warrants a treatment paradigm commensurate with the significant risk of mortality.

External-Beam Radiation Added to ADT

Randomized controlled trials have demonstrated that the addition of long-term ADT to RT for locally advanced prostate cancer resulted in a substantial improvement in overall survival (OS) compared with RT alone.[7-12] Some have assumed that the benefit of combined therapy was due to ADT, and that RT contributed little. Three important prospective trials assessed the effect of RT when added to ADT. A pivotal Scandinavian multicenter trial (SPCG-7/SFUO-3[13]) randomized 875 men with locally advanced prostate cancer to endocrine therapy alone versus the same endocrine therapy combined with RT. At 10 years, the addition of RT was found to substantially reduce the rate of PSA progression

from 74.7% in the endocrine therapy group to 25.9% in the combined therapy group. More significantly, endocrine therapy plus RT resulted in a significant reduction in both prostate cancer–specific mortality at 10 years (absolute difference = 12.0%; relative risk = 0.44) and overall mortality (absolute difference = 9.8%; relative risk = 0.68).

A similar Intergroup trial confirmed the pronounced improvement in outcomes with the addition of RT to endocrine therapy.[14] In this trial, 1205 men were randomized to lifelong ADT alone or to RT plus lifelong ADT. At 8 years, combined RT and ADT resulted in reduced disease progression (biochemical and local), disease-specific mortality (absolute difference = 20%; hazard ratio [HR] = 0.46), and overall mortality (absolute difference = 6%; HR = 0.70). In the ADT-alone group, 10% received delayed RT for local progression, suggesting that these results may underestimate the benefit of RT.[15,16]

Notable differences exist between the patients enrolled and the treatments provided in the Scandinavian[13] and NCIC/MRC trials.[15] Patients included in the NCIC/MRC study had a less favorable prognosis than the Scandinavian trial, in which 20% of patients had intermediate risk disease, and patients with PSA greater than 11 ng/mL were surgically staged, with exclusion of patients with positive lymph nodes. In contrast, all patients included in the NCIC/MRC trial had high-risk disease, some of whom likely had occult nodal involvement. While the NCIC/MRC trial treated patients with lifelong ADT using either a luteinizing hormone-releasing hormone (LHRH) agonist or orchiectomy, the Scandinavian trial used 3 months of total androgen blockade followed by anti-androgen therapy until progression or death. Despite these differences, the frequency of biochemical failure and the relative benefit observed with the addition of RT were similar in the 2 trials.

In a third trial from France, 264 men with locally advanced disease were randomized to 3 years of ADT with an LHRH agonist versus the same ADT with RT.[17] After 5 years, combined therapy resulted in significantly decreased clinical and biochemical progression, as well as reduced incidence of metastatic progression. There were no significant differences observed in disease-specific survival (DSS) or OS, likely related to the small sample size and relatively short follow-up interval.

Taken together, these 3 similarly designed trials all support substantial improvements in outcome with the addition of RT to ADT for men (median age, 70 years) treated for high-risk localized prostate cancer.

The RT delivered in each of these 3 key trials was very similar, although with important differences from contemporary prostate RT. The dose of radiation delivered to the prostate was 65 to 70 Gy using 3-dimensional conformal techniques, which would be considered low-dose RT by modern standards. In each of the trials, as expected, patients who received RT experienced a higher rate of acute urinary and bowel toxicity. The negative effect of RT on bowel function was modest, with recovery of baseline function common at 36 months.[15] Serious long-term genitourinary or gastrointestinal toxicity from RT was uncommon. For instance, in the Intergroup study, patients on ADT plus RT reported a higher frequency of grade 1-2 adverse events (AEs) related to bowel toxicity, but only 2 of 589 patients had grade 3 or greater diarrhea at 24 months after RT.[14] Three years after completing RT, there were no significant differences in patient-reported outcomes of diarrhea, bowel or rectal toxicity, urinary functioning, or overall physical functioning between the 2 arms. In the Scandinavian trial, after 5 years, significantly more patients in the endocrine-plus-RT group had urinary incontinence (3% ADT alone vs 7% ADT plus RT), urgency (8% ADT alone vs 14% ADT plus RT), urethral stricture (0% ADT alone vs 6/329 [2%] ADT plus RT), and erectile dysfunction (81% ADT alone vs 89% ADT plus RT). There were no significant differences in gastrointestinal symptoms at 5 years, global quality of life at 4 years, or serious AEs. Patient-rated acceptability of the outcome from RT was over 85%.[13] Overall, the side effects associated with RT were modest, and the incidence of severe toxicity was low.

Furthermore, contemporary treatment techniques, including intensity-modulated radiation and image-guided radiation, allow for an increase of the prostate radiation dose to 78 Gy or higher, which is associated with improved biochemical control.[18-20] Prospective data also suggest that the higher dose of radiation can be delivered with minimal toxicity, provided that threshold doses to organs at risk are not exceeded.[21,22] Therefore, the substantial benefit observed with adding RT and the modest toxicity suggest that concerns about toxicity from RT are not a reason to withhold treatment.

Controversies in RT for High-Risk Prostate Cancer

Undertreatment of High-Risk Prostate Cancer in the Elderly

In the clinical case described above, one argument might be that the patient at age 77 years is too old to conceivably benefit from the addition of RT to ADT, and that the risk of extra toxicity is not warranted. Importantly, the substantial DSS and OS benefits observed in the 3 randomized trials of ADT with or without RT were also recently replicated in a population-based observational study using SEER-Medicare data.[23] The authors performed 3 separate analyses, all in men 65 years or older. First, they limited results to those under age 70 years who were similar in character to participants in the phase III trials. Second, they limited the analysis to those over age 75 years as an elderly cohort. Finally, they performed the analysis only in those with PSA-screened disease, reflecting common current clinical practice. Reassuringly, from the first analysis they observed that the outcomes seen in selected patients enrolled in clinical trials with improvements in both DSS and OS were also applicable to a similar group of men receiving care in the community.

More important, the second analysis extended the generalizability of these findings to men older than 75 years, who were found to have a 50% reduction in the risk of dying from prostate cancer (HR = 0.51) and a 40% reduction in all-cause mortality (HR = 0.63). The importance of this finding is underscored by the observation that older men are more likely to have high-risk disease,[24] and account for approximately half of deaths as a result of prostate cancer.[25] In light of these findings, it is concerning to note the prevalence of age-dependent bias against local therapy for high-risk prostate cancer, with 67% of men older than 75 years receiving primary ADT or no therapy at all and only 33% receiving any local therapy.[24] Furthermore, undertreatment of high-risk prostate cancer is a growing problem, with increasing use of primary ADT monotherapy over time.[26]

Pelvic Nodal Radiation

The decision to treat the pelvic lymph nodes with RT remains an area of controversy. Both the NCIC/MRC trial[15] and the French trial[17] included treatment of the pelvic lymph nodes to 45-46 Gy, whereas the Scandinavian trial,[13] in which patients with PSA greater than 11 ng/mL were surgically staged and excluded if found to have positive lymph nodes, did not. In prospective trials that evaluated the role of ADT added to RT, 4[7-10] out of 6 studies[11,12] included whole-pelvis radiation therapy (WPRT). Some have suggested that this treatment approach should, therefore, serve as the precedent for appropriate clinical practice. However, results from 2 randomized trials specifically evaluating the role of WPRT have not yet provided clear evidence to support this practice. In GETUG-01, pelvic nodal radiation was well tolerated but did not improve progression-free survival (PFS).[27] In RTOG 9413, after 4 years WPRT was associated with improved PFS,[28] though this difference was no longer significant with longer follow-up.[29] The results were suggestive of an interaction between the timing of ADT and the size of the radiation field, with a trend toward improved PFS when neoadjuvant ADT was used in conjunction with WPRT versus the same treatment with RT to the prostate alone. The authors suggest that in light of the radiation field size used in the clinical trials of RT ± ADT, WPRT and long-term ADT remains the standard.

Some have argued that patients treated in the PSA era have lower risk of nodal involvement than those enrolled in clinical trials from the 1980s and early 1990s, and that the 2 large prospective randomized trials specifically designed to evaluate WPRT have not provided sufficient evidence to justify the uniform use of a pelvic field.[30] However, it is of note that patients in the GETUG-01 trial likely had a low risk of pelvic nodal involvement, which weakens the conclusion about the lack of benefit from WPRT. Thus, the question of whether elective pelvic nodal radiation provides a significant clinical benefit remains an area of controversy,[31] with resultant variability in clinical practice patterns.

Radiation for Node-Positive Disease

The role of RT for patients with involved pelvic lymph nodes has also yet to be clearly defined, although increasing evidence supports a role for combined ADT plus RT. Patients with nonmetastatic, node-positive disease (N1 M0) are categorized as stage IV and are often grouped together with patients who have metastatic disease,[32] although a small number of patients with node-positive disease were included in the prospective clinical trials adding ADT to RT.[33,34] Further, in patients who undergo radical prostatectomy and are found to have positive lymph nodes, hormonal therapy (HT) alone is an established treatment with demonstrated improvement in DSS and OS.[35] Nevertheless, the role of RT in patients with positive nodes either with or without surgery is at this point unclear.

A retrospective series from an Italian group evaluated the role of RT in patients who had pathologically positive pelvic lymph nodes discovered at the time of lymphadenectomy. In a matched analysis of patients treated with HT alone versus HT plus RT, the addition of RT was associated with improved biochemical relapse-free survival, DSS, and OS.[36,37] These findings were replicated in a retrospective series of 255 patients from MD Anderson Cancer Center, which found a substantial improvement in disease control and survival when RT was added to androgen ablation.[38] A similar magnitude of benefit for combined ADT plus RT relative to ADT alone has also been found in observational data from population-based studies.[39,40]

While there has not been a formal randomized trial evaluating the role of RT in patients with node-positive disease, an early trial of RT alone compared with RT plus ADT, RTOG 85-31,[33] included 173 patients with histologically involved lymph nodes who were randomized. Combination therapy was associated with a significant improvement in all endpoints analyzed: biochemical control, metastatic failure, disease-specific failure, and OS. The STAMPEDE trial[41] included 155 prospectively enrolled, nonrandomized patients with N+M0 disease who were treated with either HT alone or the combination of RT plus HT. After 2 years, failure-free survival was significantly greater for patients who received RT. Taken together, these results seem to indicate that RT contributes significantly to improved outcomes in patients with node-positive, nonmetastatic prostate cancer, and that many such patients may achieve long-term survival and are likely curable with aggressive therapy.[42] Use of intensity-modulated radiation may improve the therapeutic ratio for nodal treatment compared with WPRT by allowing delivery of nodal treatment with limited AEs.[43]

Conclusion

For the 77-year-old man wishing to minimize the cost and inconvenience of treatment, based on the evidence described here, there is little question regarding the essential role of RT when added to ADT in prolonging survival for patients with high-risk

and locally advanced prostate cancer. Taken together, the 3 randomized trials described demonstrate that the addition of RT is associated with an approximate two-thirds reduction in biochemical recurrence, a doubling of DSS, and a resultant significant improvement in OS. These findings seem especially applicable to elderly men, who have a greater probability of being diagnosed with high-risk prostate cancer, yet are also more likely to be undertreated with ADT monotherapy. In men who are able to tolerate ADT, careful consideration should also be given to treating with RT, which is associated with substantial improvements in DSS and OS, and can be delivered with minimal morbidity using modern treatment techniques.

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Disclosures: Dr Hamstra has served as a consultant for Augmenix, on advisory boards for Medivation and Johnson & Johnson, and as a speaker for Varian Medical Systems. Dr Shumway has no relevant conflicts of interest to disclose.
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REFERENCES

1. Moyer VA. Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *Ann Intern Med*. 2012;157:120-134.
2. Jacobs BL, Zhang Y, Schroeck FR, et al. Use of advanced treatment technologies among men at low risk of dying from prostate cancer. *JAMA*. 2013;309:2587-2595.
3. Klotz L, Vesprini D, Sethukavalan P, et al. Long-term follow-up of a large active surveillance cohort of patients with prostate cancer. *J Clin Oncol*. 2015;33:272-277.
4. Siegel R, Naishadham D, Jemal A. Cancer statistics, 2013. *CA Cancer J Clin*. 2013;63:11-30.
5. Albertsen PC, Hanley JA, Gleason DF, et al. Competing risk analysis of men aged 55 to 74 years at diagnosis managed conservatively for clinically localized prostate cancer. *JAMA*. 1998;280:975-980.
6. Lu-Yao GL, Albertsen PC, Moore DF, et al. Outcomes of localized prostate cancer following conservative management. *JAMA*. 2009;302:1202-1209.
7. 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;49:937-946.
8. Pilepich MV, Winter K, John MJ, et al. Phase III radiation therapy oncology group (RTOG) trial 86-10 of androgen deprivation adjuvant to definitive radiotherapy in locally advanced carcinoma of the prostate. *Int J Radiat Oncol Biol Phys*. 2001;50:1243-1252.
9. Hanks GE, Pajak TF, Porter A, et al. Phase III trial of long-term adjuvant androgen deprivation after neoadjuvant hormonal cytoreduction and radiotherapy in locally advanced carcinoma of the prostate: the Radiation Therapy Oncology Group Protocol 92-02. *J Clin Oncol*. 2003;21:3972-3978.
10. Bolla M, Collette L, Blank L, et al. Long-term results with immediate androgen suppression and external irradiation in patients with locally advanced prostate cancer (an EORTC study): a phase III randomised trial. *Lancet*. 2002;360:103-106.
11. Denham JW, Steigler A, Lamb DS, et al. Short-term neoadjuvant androgen deprivation and radiotherapy for locally advanced prostate cancer: 10-year data from the TROG 96.01 randomised trial. *Lancet Oncol*. 2011;12:451-459.
12. D'Amico AV, Chen MH, Renshaw AA, et al. Androgen suppression and radiation vs radiation alone for prostate cancer: a randomized trial. *JAMA*. 2008;299:289-295.
13. Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. *Lancet*. 2009;373:301-308.
14. Mason MD, Parulekar WR, Sydes MR, et al. Final report of the Intergroup randomized study of combined androgen-deprivation therapy plus radiotherapy versus androgen-deprivation therapy alone in locally advanced prostate cancer [published online February 17, 2015]. *J Clin Oncol*. 2015. pii:JCO.2014.57.7510.
15. Warde P, Mason M, Ding K, et al. Combined androgen deprivation therapy and radiation therapy for locally advanced prostate cancer: a randomised, phase 3 trial. *Lancet*. 2011;378:2104-2111.
16. Cooperberg MR. High-risk prostate cancer: treat the prostate. *Lancet*. 2011;378:2056-2057.
17. Mottet N, Peneau M, Mazeron JJ, et al. Addition of radiotherapy to long-term androgen deprivation in locally advanced prostate cancer: an open randomised phase 3 trial. *Eur Urol*. 2012;62:213-219.
18. Kuban DA, Tucker SL, Dong L, et al. Long-term results of the MD Anderson randomized dose-escalation trial for prostate cancer. *Int J Radiat Oncol Biol Phys*. 2008;70:67-74.
19. Viani GA, Stefano EJ, Afonso SL. Higher-than-conventional radiation doses in localized prostate cancer treatment: a meta-analysis of randomized, controlled trials. *Int J Radiat Oncol Biol Phys*. 2009;74:1405-1418.
20. Zietman AL, Bae K, Slater JD, et al. Randomized trial comparing conventional-dose with high-dose conformal radiation therapy in early-stage adenocarcinoma of the prostate: long-term results from Proton Radiation Oncology Group/American Col-

lege of Radiology 95-09. *J Clin Oncol*. 2010;28:1106-1111.
21. Michalski JM, Yan Y, Watkins-Bruner D, et al. Preliminary toxicity analysis of 3-dimensional conformal radiation therapy versus intensity modulated radiation therapy on the high-dose arm of the Radiation Therapy Oncology Group 0126 prostate cancer trial. *Int J Radiat Oncol Biol Phys*. 2013;87:932-938.
22. Hamstra DA, Conlon AS, Daignault S, et al. Multi-institutional prospective evaluation of bowel quality of life after prostate external beam radiation therapy identifies patient and treatment factors associated with patient-reported outcomes: the PROSTQA experience. *Int J Radiat Oncol Biol Phys*. 2013;86:546-553.
23. Bekelman JE, Mitra N, Handorf EA, et al. Effectiveness of androgen-deprivation therapy and radiotherapy for older men with locally advanced prostate cancer [published online March 1, 2015]. *J Clin Oncol*. doi:10.1200/JCO.2014.57.2743.
24. Bechis SK, Carroll PR, Cooperberg MR. Impact of age at diagnosis on prostate cancer treatment and survival. *J Clin Oncol*. 2011;29:235-241.
25. Scosyrev E, Messing EM, Mohile S, et al. Prostate cancer in the elderly: frequency of advanced disease at presentation and disease-specific mortality. *Cancer*. 2012;118:3062-3070.
26. Cooperberg MR, Broering JM, Carroll PR. Time trends and local variation in primary treatment of localized prostate cancer. *J Clin Oncol*. 2010;28:1117-1123.
27. Pommier P, Chabaud S, Lagrange JL, et al. Is there a role for pelvic irradiation in localized prostate adenocarcinoma? Preliminary results of GETUG-01. *J Clin Oncol*. 2007;25:5366-5373.
28. Roach M 3rd, DeSilvio M, Lawton C, et al. Phase III trial comparing whole-pelvic versus prostate-only radiotherapy and neoadjuvant versus adjuvant combined androgen suppression: Radiation Therapy Oncology Group 9413. *J Clin Oncol*. 2003;21:1904-1911.
29. Lawton CA, DeSilvio M, Roach M 3rd, et al. An update of the phase III trial comparing whole pelvic to prostate only radiotherapy and neoadjuvant to adjuvant total androgen suppression: updated analysis of RTOG 94-13, with emphasis on unexpected hormone/radiation interactions. *Int J Radiat Oncol Biol Phys*. 2007;69:646-655.
30. Nguyen PL, D'Amico AV. Targeting pelvic lymph nodes in men with intermediate- and high-risk prostate cancer despite two negative randomized trials. *J Clin Oncol*. 2008;26:2055-2056; author reply 2056-2057.
31. Rosenthal SA, Sandler HM. Treatment strategies for high-risk locally advanced prostate cancer. *Nat Rev Urol*. 2010;7:31-38.
32. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology: Prostate Cancer, Version 1.2015. http://www.nccn.org/professionals/physician_gls/pdf/prostate.pdf. Accessed April 7, 2015.
33. Lawton CA, Winter K, Grignon D, et al. Androgen suppression plus radiation versus radiation alone for patients with stage D1/pathologic node-positive adenocarcinoma of the prostate: updated results based on national prospective randomized trial Radiation Therapy Oncology Group 85-31. *J Clin Oncol*. 2005;23:800-807.
34. Bolla M, de Reijke TM, Van Tienhoven G, et al. Duration of androgen suppression in the treatment of prostate cancer. *N Engl J Med*. 2009;360:2516-2527.
35. Messing EM, Manola J, Yao J, et al. Immediate versus deferred androgen deprivation treatment in patients with node-positive prostate cancer after radical prostatectomy and pelvic lymphadenectomy. *Lancet Oncol*. 2006;7:472-479.
36. Da Pozzo LF, Cozzarini C, Briganti A, et al. Long-term follow-up of patients with prostate cancer and nodal metastases treated by pelvic lymphadenectomy and radical prostatectomy: the positive impact of adjuvant radiotherapy. *Eur Urol*. 2009;55:1003-1011.
37. Briganti A, Karnes RJ, Da Pozzo LF, et al. Combination of adjuvant hormonal and radiation therapy significantly prolongs survival of patients with pT2-4 pN+ prostate cancer: results of a matched analysis. *Eur Urol*. 2011;59:832-840.
38. Zagars GK, Pollack A, von Eschenbach AC. Addition of radiation therapy to androgen ablation improves outcome for subclinically node-positive prostate cancer. *Urology*. 2001;58:233-239.
39. Rusthoven CG, Jackson MW, Amini A, et al. Lymph node-positive (N1M0) prostate cancer: an analysis of prognostic and predictive factors for men treated with and without definitive external beam radiation therapy in the United States population. *Int J Radiat Oncol*. 2014;90(suppl:S14).
40. Lin C, Gray PJ, Jemal A, et al. Radiation therapy for clinically node-positive prostate cancer and survival: results from the National Cancer Data Base. *Int J Radiat Oncol*. 2014;90 (suppl:S13-S14).
41. J James N, Spears M, Clarke N, et al. Impact of node status and radiotherapy on failure-free survival in patients with newly diagnosed non-metastatic prostate cancer: data from > 690 patients in the control arm of the STAMPEDE trial. *Ann Oncol*. 2014;25:(suppl_4):iv255-iv255. Abstract 7540.
42. Baker BR, Mohiuddin JJ, Chen RC. The role of radiotherapy in node-positive prostate cancer. *Oncol (Williston Park)*. 2015;29:108-114; 116.
43. Ashman JB, Zelefsky MJ, Hunt MS, et al. Whole pelvic radiotherapy for prostate cancer using 3D conformal and intensity-modulated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2005;63:765-771.