Commentary

Invited commentary on GETUG-AFU 16

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Comment on: Carrie C, Hasbini A, de Laroche G, *et al.* Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomised, multicentre, open-label phase 3 trial. Lancet Oncol 2016;17:747-56.

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I am grateful to accept the invitation to provide this commentary on the recently published article entitled "Salvage radiotherapy with or without short-term hormone therapy for rising prostate-specific antigen concentration after radical prostatectomy (GETUG-AFU 16): a randomized, multicenter, open-label phase 3 trial" (1). This important trial adds to the salvage radiotherapy literature which historically has been largely populated with retrospective analyses. The GETUG-AFU 16 trial observed improved progression-free survival when 6 months of goserelin was added to radiotherapy. In this short note I will provide a critical appraisal of the GETUG study, briefly describe another trial of salvage radiotherapy and androgen suppression (RTOG/NRG Oncology 96-01) and at the end describe how I incorporate the findings of each of these studies into my practice.

Biochemical recurrence (BCR) is a common occurrence following radical prostatectomy (RP), observed in 25–50% of men depending on the risk group (2). The natural history of BCR following RP is heterogeneous. An early report from the Johns Hopkins group found that disease-specific mortality within 5 years of BCR ranged from 2% to 85% depending on Gleason score, prostate-specific antigen (PSA) doubling time and interval from RP to BCR (3). As a result treatment recommendations for BCR following RP include observation, androgen suppression alone or salvage radiation therapy with or without androgen suppression. Although level I evidence is lacking, retrospective series have suggested that salvage radiotherapy reduces distant metastases and prostate cancer mortality (4). A recent retrospective series from the Mayo clinic has reported a reduction in distant metastases, cause-specific and overall mortality when salvage radiotherapy is given at a PSA of ≤0.5 ng/mL (5).

The participants enrolled on the GETUG-AFU 16 trial were status-post RP with a serum PSA level between 0.2 and <2.0 ng/mL. This study then is one of the few randomized trials of salvage radiotherapy as opposed to adjuvant radiotherapy. The findings are therefore more germane to men referred by urologists in the United States where adjuvant radiotherapy is rarely performed (6). The interquartile range (IQR) for baseline PSA at the time of randomization on the GETUG trial was 0.2–0.5 ng/mL. A recent multi-institutional cohort found the PSA at the time of salvage radiotherapy to be significantly higher (IQR 0.3–1.1) (7). The men in the GETUG study, therefore, were referred for radiation therapy relatively early.

It is also important to highlight that the study required that the PSA had been <0.1 ng/mL for at least six months after surgery. It is clear that men with detectable PSA levels within the first 6 months of RP (detectable nadir following RP) have a particularly poor prognosis. For example, in RTOG 0621, a single arm Phase II trial combining salvage RT, 6 months of androgen suppression and adjuvant docetaxel, the 5-year rate of distant metastasis patients was greater than 25% in patients with a PSA nadir of ≥0.2 ng/mL following RP (8). This high rate of systemic progression justifies excluding these patients from the GETUG study, but combined with the low baseline PSA levels at randomization, it is likely that the number of distant metastatic events will be low perhaps precluding finding differences in more clinically relevant endpoints in

the future.

The radiotherapy protocol in GETUG-AFU 16 required that all patients were treated with 66 Gray (Gy) to the prostate bed using three-dimensional conformal radiotherapy (3DCRT) or intensity-modulated radiation therapy (IMRT) with the vast majority (>95%) receiving 3DCRT. Of note, the pelvic lymph nodes were electively irradiated to 46 Gy in 16% of patients; a variation called for in the protocol if the patient did not have a lymph node dissection with the RP or if the risk of nodal involvement was greater than 15% according to the Partin table. This percentage is remarkably similar to the rate of pelvic lymph node treatment reported in a recent multi-institutional cohort (7). At present the value of elective pelvic lymph node irradiation has not been established but is being tested in RTOG 0534 (NCT00567580). This trial has recently been closed to accrual but results will not be available for several years. In summary, the men enrolled on the GETUG trial have more favorable disease than the typical patient referred for salvage radiotherapy which makes the principal finding of great interest.

RTOG/NRG Oncology 9601 has been presented but has yet to be published (the manuscript is in press at *New England Journal of Medicine* according to authors). The design is similar to the GETUG trial in that it includes men with BCR following RP and examines the value of androgen suppression added to salvage radiotherapy. There are however important differences between the two studies. The most obvious differences are the androgen suppression used (agent and duration), the length of follow-up and the primary endpoint. The hormonal therapy used in the GETUG study was 6 months of goserelin delivered in two 3-month injections started on the first day of irradiation. The RTOG used bicalutamide 150 mg po daily (or placebo) for 24 months beginning during irradiation. The median follow-up for the GETUG study is 63 months (IQR 56–75 months) which is considerably shorter than the 13-year median follow-up in the RTOG study. The primary endpoint for the GETUG study was progression free survival while the primary endpoint of the RTOG study was overall survival. Although it is more subtle the patient populations are different. Specifically, the IQR of the baseline PSA in the GETUG study was 0.2–0.5 ng/mL which is much lower than that reported on the RTOG/NRG Oncology 96-01 study (0.4–1.1 ng/mL) and the RTOG study allowed for PSA to be as high as 4.0 compared to 2.0 in the GETUG study. This difference makes it likely that patients on the GETUG study will be less likely to develop distant metastases and subsequent prostate cancer death than men enrolled on the RTOG study.

The most important finding of the RTOG study is that 24 months of bicalutamide added to salvage radiotherapy improved overall survival at ten years [82% *vs.* 78%; HR 0.75 (95%CI, 0.58–0.98)]. This improvement was driven by a reduction in prostate cancer death at ten years [10% *vs.* 5%; HR 0.49 (0.32–0.74)]. The rate of distant metastases at ten years was reduced as well [19% *vs.* 11%; HR 0.63 (0.46–0.87)]. Exploratory subgroup analyses demonstrated that the benefit of bicalutamide was most evident in men with Gleason scores of 7 or higher, pre-radiotherapy PSA values of 0.7 or greater and positive surgical margins. The GETUG investigators write in their discussion that "longer follow-up is needed to establish the effect of this therapeutic strategy on overall survival". Based on the favorable patients enrolled I am skeptical that the study is sufficiently powered for that endpoint.

So we have two studies that show improved outcomes with the addition of hormonal therapy to salvage radiotherapy in men with detectable PSA levels. Does this mean that all men with BCR after RP should be treated with hormonal therapy? I don't believe so. In those men with very high risk features (PSA nadir >0.2, pre-radiotherapy PSA of >1 and Gleason score of 8–10) I recommend 24 months of hormonal therapy combined with radiotherapy based on the results from RTOG 9601. At the other extreme, for example a man with a positive surgical margin, a PSA that has been undetectable for 8 years and a pre-radiotherapy PSA of 0.2 ten years after RP, I would not recommend androgen suppression; and depending on the age of the man I may not recommend salvage radiotherapy as he is likely to remain free of clinical progression for several years. For the man that falls between these extremes I engage in shared decision making. I inform the man that a short course of androgen suppression (6 months) added to salvage radiotherapy will decrease the likelihood of subsequent BCR but may not improve their survival. They can then decide whether they are willing to accept mild short-term toxicity of androgen suppression for the possibility of reducing distant metastases and prostate cancer mortality.

Acknowledgements

None.

Footnote

Conflicts of Interest: The author has no conflicts of interest to declare.

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