

Platinum Priority

Reply from Authors re: Michel Bolla. The Moving Landscape of Locally Advanced Prostate Cancer: Combination of External Irradiation and Endocrine Treatment and/or Multimodal Approach. *Eur Urol* 2012;62:220–1

Locally Advanced Prostate Cancer: Optimal Locoregional Control Matters

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Several years ago, the European Organization for Research and Treatment of Cancer 22863 trial initiated a new standard for locally advanced prostate cancer. Adding long-term systemic androgen-deprivation therapy (ADT) to the standard “old-fashioned” pelvic and prostate radiotherapy was associated with a very significant improvement in survival [1]. This was later confirmed by the Radiation Therapy Oncology Group 8531 trial. Both trials defined a new standard, as highlighted in the guidelines [2]. It was also later clarified that the ADT had to be long term, ideally 3 yr [3].

Following the first trial, the real impact of radiotherapy associated with long-term ADT was questioned. A clear answer is now available based on three prospective randomized trials [4–6]. In patients with an expected survival of several years (>4–5 yr), the combined treatment is essential, even if a survival benefit was observed in only two trials, the third one [6] having the shortest follow-up (median follow-up: 67, 72, and 91 mo, respectively). These trials highlight the major role of local treatment in patients with clinically locally advanced disease. Although the three trials had no uniform inclusion criteria, most patients were considered locally advanced based on their T status (T3/T4) or with an aggressive Gleason score, and all were stratified as N0 based on computed tomography (CT) or magnetic resonance imaging (MRI).

We fully agree with Bolla's comments [7] that these trials need to be put in the current context, and we agree with many of his opinions. However, some statements deserve a response, such as that MRI provides better local staging and the practical attitude expressed regarding the suggested initial nodal dissection. We would like to add caution to his view regarding the usually performed prostate and pelvic MRI. In expert centers, a multiparametric MRI seems to improve local and nodal staging, but its added value outside these expert centers remains controversial [2] and far from effective.

We do not agree with his request for an initial extended node dissection in young patients when all the available data come from patients without any nodal dissection and with whole pelvic irradiation. In fact, this extended dissection is the only way to characterize nodal status. This dissection is defined based on clear anatomic landmarks but not from clear-cut numbers of nodes to be removed. When a CT is N0, it just means that patients do not have nodes >1 cm. The lack of enlarged nodes rules out bulky disease, but multiple positive nodes might still be present. In locally advanced disease, such as those considered in the three previously mentioned trials [4–6], we must acknowledge that at least 30–50% of the included N0 patients were in fact pN+, based on results from extended nodal dissection [2,8]. Bolla speculated that if a minimal amount of involvement is present, the radiation could be limited to the prostate only, based on the finding from a retrospective cohort (reference 7 in Bolla [7]). In addition to the unclear definition of “a minimal amount” from a “significant number” removed, this is only speculative. The effectiveness of an extended nodal dissection in terms of staging improvement is clear. However, the improvement in survival observed in the case of minimal nodal improvement is so far at best hypothetical and has never been clearly confirmed. The standard of care in node-positive situations remains controversial. If a massive involvement is observed, immediate adjuvant lifelong ADT is the standard of care [2]. The available data are not so clear in the case of minimal involvement. After an extended node dissection, Briganti et al. suggested a benefit for an adjuvant combination of ADT and pelvic irradiation compared with the standard ADT only in pN+ patients [9]. This benefit was observed in the entire cohort and also in those with fewer than two positive nodes (log-rank test: $p = 0.006$; hazard ratio [HR]: 2.01) or with massive involvement (log-rank test: $p = 0.003$; HR: 3.9). At least, this suggests missed nodes even after an extended dissection. Regarding pN0 status, the staging is also probably not as accurate as one could believe. Based on improved nodal analysis through immunohistochemistry using antibodies to cytokeratin and prostate-specific antigen (PSA) [10], patients with occult lymph node metastases detected through this method (13.3% of pN0 patients) had the same prognosis as those with histologically confirmed pN+. The added specific toxicity from the pelvic radiotherapy, even if real, does not appear to be that high [2] and must be balanced against the potential added survival seen in advanced situations. Finally, only prospective trials will definitively answer the question of pelvic irradiation in pN0 patients in locally advanced disease where the available data clearly suggest the importance of optimal pelvic control, probably with the use of radiotherapy in locally advanced N0 disease.

As long as optimal locoregional control is the key, these trials also raise the question of the real place for a radical prostatectomy as a local treatment. In locally advanced disease, surgery is an option in selected

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patients, often in a multimodal approach. Only randomized control trials will confirm the added value of the combination of surgery and a systemic hormonal treatment, already demonstrated with radiotherapy. This multimodal attitude is so far only suggested from retrospective cohorts. Such trials are under way, such as the AFU-GETUG 20 for postoperative high-risk patients with a postoperative undetectable PSA.

Conflicts of interest: The authors have nothing to disclose.

References

- [1] 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;337:295–300.
- [2] Heidenreich A, Bastian PJ, Bellmunt J, et al. Guidelines on prostate cancer. European Association of Urology Web site. http://www.uroweb.org/gls/pdf/08%20Prostate%20Cancer_LR%20March%2013th%202012.pdf. Updated 2012.
- [3] 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;360:2516–27.
- [4] 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;373:301–8.
- [5] 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;378:2104–11.
- [6] Mottet N, Peneau M, Mazon J-J, Molinier V, Richaud P. Addition of radiotherapy to long-term androgen deprivation in locally advanced prostate cancer: an open randomised phase 3 trial. *Eur Urol* 2012;62:213–9.
- [7] Bolla M. The moving landscape of locally advanced prostate cancer: combination of external irradiation and endocrine treatment and/or multimodal approach. *Eur Urol*. In press. <http://dx.doi.org/10.1016/j.eururo.2012.04.040>.
- [8] Heidenreich A, Ohlmann CH, Polyakov S. Anatomical extent of pelvic lymphadenectomy in patients undergoing radical prostatectomy. *Eur Urol* 2007;52:29–37.
- [9] 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;59:832–40.
- [10] Pagliarulo V, Hawes D, Brands FH, et al. Detection of occult lymph node metastases in locally advanced node-negative prostate cancer. *J Clin Oncol* 2006;24:2735–42.

<http://dx.doi.org/10.1016/j.eururo.2012.05.010>

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