

We should not settle for low-level evidence but should always use the best available evidence

To the editor: We would like to thank Dr. Mirza [1] for his editorial in response to our paper [2] on “Ultrasound guided conformal brachytherapy of cervix cancer: survival, patterns of failure, and late complications.” He has raised several questions about our study, which we would like to address. Firstly, we would like to clarify that this study is based on data from our prospective unit database and is not, as stated by Dr. Mirza a retrospective study. This is an ethics-approved database into which baseline, treatment and outcome data about all patients referred to our unit for radiotherapy were entered prospectively. Toxicities were scored according to modified World Health Organization/Radiation Therapy Oncology Group criteria. We have reported three categories of toxicities to organs at risk, namely bladder, small and large bowel, and vagina.

Q: Can we further improve local control? Patterns of failure at local site are not addressed.

A: Of course we can improve local control further but the critical question is whether this will translate into improved cure rates. A straightforward way of increasing local control would be to increase the brachytherapy dose to the primary site. This is being done in some European countries by dose escalation using magnetic resonance imaging guided conformal brachytherapy where target doses in excess of 95 Gy (EQD2) leading to local control of >95% has been achieved [3].

In another study, in an ultimate effort to control local disease, 58% of treated patients had elective hysterectomy performed following the completion of curative radiotherapy [4]. However, in neither case was overall survival better than we have reported.

In our earlier publication, we had compared the treatment of cervix cancer patients using low dose rate brachytherapy (LDR) and high dose rate brachytherapy (HDR) conformal brachytherapy. In that paper we had specifically discussed the

dose escalation issue [5].

Prescribed dose in high dose rate conformal brachytherapy (HDRc) patients and the patients treated with LDR was 80 Gy10 to the outer contour of target and point A respectively. HDRc patients received a mean dose of 11 Gy less to point A than those treated by LDR for similar local failure rates. Because local tumor parameters were matched in both groups, it appears the brachytherapy target in LDR-treated patients received a higher dose at least in the plane of point A. This means three things: (1) In a target of variable geometry as applied in HDRc, a single dose point (such as point A) does not reflect the minimum covering target isodose. Point A is unrelated to the target volume. (2) Curable tumors are controlled by a minimum dose of 70 to 80 Gy10; a dose greater than this would be wasted. Not only was the local control similar in both groups, but the median time to failure was also similar at 6 and 7 months. (3) Brachytherapy target, as defined in this study, is satisfactory. This last point is better explained by further dividing the HDRc-treated patients into two groups. Patients in group 1 had smaller target volume and received <72.8 Gy10 to point A. The average target dose in group 1 was 79.2 Gy10. Patients in group 2 had larger target volumes and received >72.8 Gy10 to point A. The average target dose in group 2 was 81.3 Gy10. Of the 13 primary site failures, only 2 failed in the lower dose group 1, whereas 11 failed in the higher dose group 2. Failure rates at other sites were also higher in the high-dose group, suggesting that tumors that shrink poorly have a bad prognosis. Because isolated primary site failures were rare and time to failure at other sites was not dependent on point A dose, we believe that increasing dose to brachytherapy target may not translate in improved survival.

In fact in our present publication, we have discussed that it is generally agreed that local control of the primary cancer is associated with a higher survival in cancer patients. With the application of precision radiotherapy in cervical cancer, it has now become possible to achieve adequate locoregional control while limiting the treatment related side effects. Looking at our patterns of failure we had hypothesized that due to tumour cell dissemination during radiotherapy, beyond a certain limit survival would not improve even if we were able to achieve a complete control of the disease within the radiation field. The paragraph containing this hypothesis had to be removed following peer-review of our manuscript. Here we reproduce the paragraph submitted in our ‘original’ version.

In patients where nodal metastases were present before treatment, it would be reasonable to assume that the tumor cells had access to functional lymphatics. Tumor cells were able to survive in lymphatics and upon reaching lymph-nodes; these cells remained capable of dividing and producing a colony. During a course of radiotherapy, the tumor gets progressively disrupted as it is being sterilised, and the same physiological processes, now accelerated due to the effects of radiation on the tumor and normal tissue stroma, come into effect. Partially irradiated tumor cells in node positive patients follow the already established path through the lymphatics. Tumor cells along with the increased lymph flow get drained into higher echelons of nodes (i.e., outside the field), and through inter-tissue lymphatico-venous anastomosis [6] get distributed regionally and systemically. After all, how and where can a 6 to 8 cm tumour physically disappear within four to six weeks during the concurrent chemo-radiotherapy, but for the clearance, at least in part, by the lymphatic system? Phenomena such as interstitial haemorrhage, damaged and dead cells or sentinel lymph node tracer from the interstitium, all are cleared by lymphatics. In cervix cancer this phenomenon was first observed by Delpech et al. [7] in patients with FIGO stage 1B2 and 2, who had a full course of curative chemoradiation therapy followed by hysterectomy and lymphadenectomy. Delpech et al. [7] were surprised to find more than twice the incidence of para-aortic nodal involvement (18%) following a full course of chemoradiation therapy, in comparison to 8% patients with positive para-aortic nodes in similar stages whom they had treated earlier with primary surgery [8].

The point we wish to make is that if clonogenic cells were to escape from the radiation field before the completion of treatment than beyond a certain point the local control will have no effect on overall recurrence unless combined with more effective systemic therapy. This hypothesis is consistent with observations reported in the present study. More aggressive therapy at the primary site has been shown to be associated with increased morbidity without any improvement in OS [9]. Indeed following such numerous discussions at our cancer centre, our colleagues have been able to demonstrate that mobilization of viable tumor cells into the circulation occurs early during radiation therapy for lung cancer [10].

Q: They describe the number of central relapses and that the frequency of these relapses is comparable to earlier reported series though I miss the information of where exactly relapse occurred?

A: We have not used the term 'central relapse.' We have specifically defined primary site failure as failure in the cervix and uterus. Vaginal, parametrial and pelvic nodal failure if they

occurred were collectively defined as pelvic failures. We could look more specifically if the relapses tended to occur at the rim of the tumour or the most bulky site of initial disease as all our patients with the so called "central failure" had positron emission tomography performed to assess the suitability for salvage of the recurrent tumours.

Q: One possibility can be to modify target dose (higher external beam radiation therapy dose to some area of tumor) by performing dose-painting treatment plans.

A: This is an interesting theoretical concept described by Bentzen [11] in 2005. It only deals with the hypothetical control of gross disease that can be imaged. It does not deal with occult tumours, lymphovascular space invasion and indeed tumour dissemination during radiotherapy. In any case we have not seen any publications documenting improved survival following application of 'dose painting.'

Finally, Dr. Mirza asks if we should really draw any firm conclusions from our analysis and whether any further studies are planned. We would contend that our results support our use of ultrasound-guided conformal brachytherapy to produce rates of local control and overall survival that are as good as any reported in the literature. Analysis of our database has allowed us to determine that the real problem is not gaining local control but in fact that most patients who relapse die from the development of distant metastatic disease. This observation has resulted in us developing and activating the Gynecologic Cancer InterGroup (GCIg) OUTBACK trial. This randomised phase 3 trial, led by the Australia New Zealand Gynaecological Oncology Group (ANZGOG) is testing if overall survival rates will be improved by the addition of adjuvant chemotherapy with carboplatin and paclitaxel following standard chemoradiation therapy for locally advanced cervical cancer.

CONFLICT OF INTEREST

No potential conflict of interest relevant to this article was reported.

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