

## The challenges of treating locally advanced cervix carcinoma in resource limited settings – what are the options?

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Delivery of oncological care in Southern Africa remains a challenge for us all with long surgical waiting lists, radiotherapy waiting lists, stock-outs of chemotherapy and staff shortages to mention just a few. Many of us make modifications to internationally accepted protocols to adapt to our environments, for example the use of hypofractionation, excluding cisplatin in Stage IIIB patients, neoadjuvant chemotherapy and stratification of patients based on risk factors such as hydronephrosis. What has remained unanswered in many scenarios is whether there is any evidence-base to these decisions.

The oncology department at Tata Memorial Medical Centre in Mumbai, India published two vital studies in February this year. The first looks at the value of addition of cisplatin to radical radiotherapy in Stage IIIB cervical cancer patients – we have been eagerly waiting for the study results to mature.<sup>1</sup> The second examines the use of neoadjuvant chemotherapy in IB, IIA and IIB cervix cancer patients prior to surgery versus chemoradiation alone.<sup>2</sup> Both these studies are important for those of us who work in a similar environment to our Indian colleagues who face the same challenges of access to treatment, patient access to medical centres and multiple co-morbidities. The outcomes of these studies can thus be extrapolated to our own situation.

The first study examined Stage IIIB squamous cell carcinoma patients who were under the age of 65 years, HIV negative, with adequate renal function. Cases of bilateral hydronephrosis were excluded. Patients were routinely transfused to keep haemoglobin levels over 10 g/dl. Eight hundred and fifty patients (850) were randomised to receive either standard pelvic radiotherapy and brachytherapy versus the same with concurrent weekly Cisplatin. The outcomes showed a significant disease free and overall survival benefit to the addition of Cisplatin; disease free survival (DFS) 52.3% vs 43.8%, HR 0.81 and overall survival (OS) 54% vs 46%, HR 0.82. Factors affecting outcome included extent of disease and haemoglobin > 10 g/dl. This study conclusively shows the benefit of Cisplatin and should encourage us all to use the drug where available. The issue of maintaining haemoglobin levels is a challenge to many centres with blood being a scarce and expensive resource, centres in South Africa have addressed this with the use of intravenous

Iron.<sup>3</sup> What it does not answer is the issue of HIV positivity which is of particular significance in our situation. With limited single institution data available, most will treat as per their HIV negative counterparts if immunocompetent.

The second study addressed the use of neoadjuvant chemotherapy followed by surgery, versus standard chemoradiation in 'early' inoperable cervical carcinoma (IB, IIA2, IIB). The importance of this study in the region is significant. Most centres have prolonged waiting lists or alternatively no access to radiotherapy services. If these centres are able to deliver chemotherapy and have sufficient surgical skills this can be an appropriate intervention. The study from Tata Memorial randomised 633 women to either neoadjuvant carboplatin and paclitaxel for 3 cycles, versus standard chemoradiation. There was a significant number of patients in the study arm who either crossed over to primary chemoradiation (21.5%) or were in need of adjuvant radiotherapy postoperatively (32.2%), this equates to over 50% of those in the neoadjuvant chemotherapy arm. The primary outcome of DFS was in favour of the standard arm of chemoradiation, DFS 69% vs 76.7% (HR 1.38, p = 0.038). The secondary endpoint of overall survival was however not significantly different, 75.4% vs 74.4% (HR 1.025, p = 0.87). It is this outcome that will reassure those who work in centres with limited access to radiotherapy that this intervention is a viable alternative.

So where do we go from here? Both studies looked at questions that many of us have been contemplating for some time. The environment that these studies were conducted in are very similar to the southern African region with challenges with access to care. The conclusions we can draw from both outcomes is that standard chemoradiation is the most ideal treatment and must be delivered whenever possible. A recent meta-analysis of chemoradiation in locally advanced cervical carcinoma noted an increase of Grade 3/4 acute toxicity by 10.3% over radiotherapy alone.<sup>4</sup> This is not an insignificant issue; the authors highlighted the financial cost to the patient and health care system of managing increased toxicity and this should be kept in mind when implementing these regimens. One of the questions that

remain is the management of HIV positive patients and the onus is on us as regional researchers in an area of high HIV prevalence to undertake these studies. Furthermore, stratification of patients within the IIIB group is necessary to ensure maximisation of resources for those who will derive the most benefit.

### References

1. Shrivastava S, Mahantshetty U, Engineer R, et al. Cisplatin Chemoradiotherapy vs Radiotherapy in FIGO Stage IIIB Squamous Cell Carcinoma of the Uterine Cervix: A Randomized Clinical Trial. *JAMA Oncol*, 2018. Epub ahead of print.
2. Gupta S, Maheshwari A, Parab P, et al. Neoadjuvant Chemotherapy Followed by Radical Surgery Versus Concomitant Chemotherapy and Radiotherapy in Patients With Stage IB2, IIA, or IIB Squamous Cervical Cancer: A Randomized Controlled Trial. *J Clin Oncol*, 2018. Epub ahead of print.
3. Dreyer G, Mostert A, Visser C, et al. The severity and optimal management of iron deficiency and anaemia before radiation for cervical cancer at the University of Pretoria Academic Hospitals. *SAJGO*, 2017. 9(1).
4. Datta NR, Stutz E, Liu M, et al. Concurrent chemoradiotherapy vs. radiotherapy alone in locally advanced cervix cancer: A systematic review and meta-analysis. *Gynecologic Oncology* 2017. 145 (2): 374-385.