Selected Summaries

Cancer of the cervix: What is better?

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SUMMARY

In this single-centre study done over 14 years, patients with cervical cancer stage IB2 to IIB were randomized between three cycles of neoadjuvant chemotherapy (NACT) followed by surgery (radical hysterectomy) and concurrent chemoradiation (CTRT). NACT patients received three cycles of paclitaxel (175 mg/m^2) and carboplatin (area under the curve 5–6) every 3 weeks whereas for those in the CTRT arm cisplatin 40 mg/m^2 was used weekly at five doses. The primary end-point was disease-free survival (DFS, relapse or death whichever was earlier) while secondary end-points were overall survival (OS) and toxicity. The trial was designed to demonstrate 10% absolute increase in 5-year DFS in the NACT-surgery arm, assuming 65% DFS in the CTRT (control) arm (two-sided α, $p<0.05$, power 80%) with a planned sample size of 730. Accrual for the trial was stopped after 635 patients were randomized between September 2003 and February 2015, of whom there were two eligibility violations. In the remaining 633 (316 NACT-surgery, 317 CTRT, intent-to-treat population) there were 113 (17.9%) stage IB2, 158 (25.0%) IIA and 362 (57.2%) were stage IIB patients. The two arms were comparable for stage, age, haemoglobin, performance status and radiological pelvic lymph node status. At the time of analysis (data cut-off 30 March 2017), the median follow-up was 58.5 months; number of DFS events and deaths in NACT-surgery arm were 105 and 80 and those in CTRT arm were 87 and 80, respectively. Five-year DFS in the NACT-surgery arm was 67.5% and in the concurrent CTRT arm it was 72.2% (hazard ratio [HR] 1.299, 95% CI 0.977–1.725, $p<0.07$). When death due to any cause in the definition of DFS was included, there was no significant difference between the two treatment groups although there was a trend towards increased DFS with CTRT. There was no statistically significant difference in OS between the two groups. Five-year OS was 74.8% versus 74.7%, HR 1.025, 95% CI 0.752–1.398, p=0.87, respectively. Toxicity in the two arms was acceptable with some differences in pattern. The authors concluded that NACT followed by radical surgery was not superior to cisplatin-based concurrent CTRT in locally advanced squamous carcinoma of the cervix.

COMMENT

Cervical cancer is a common malignancy among women in countries with limited resources. The highest incidence rates are in Central and South America, the Caribbean, Sub-Saharan Africa and South Asia.[1] In India, its incidence varies from 13 to 24 per 100 000 women per year. While cervical cancer continues to be a common malignancy in rural India, this is preceded by breast cancer in urban India.[2] Persistent infection with human papillomavirus (HPV) and subsequent malignant transformation results in cervical cancer in almost all cases (95%). Other factors, for example, smoking, high parity and co-infection with type 2 herpes simplex or human immunodeficiency virus have been suggested to increase the risk.[3] The pivotal role of HPV in carcinogenesis has led to strategies for prevention of cervical cancer by screening and HPV vaccination using bivalent or quadrivalent vaccine. In developing and resource-limited countries where prevention is still not a focus, patients continue to present in advanced stages. Clinical presentation for cervical cancer in India has features distinct from those seen in industrialized nations; young age at diagnosis (median age 35–38 years *v*. 50–58 years, higher frequency of squamous histology (>90% *v*. ≤75%–80%) and locally advanced stage (stage IIB to IVA) in >80% of women compared to ≤50%.[4] The treatment of cervical cancer is based on the clinical staging system of the International Federation of Gynaecology and Obstetrics. Surgery is recommended for patients with early-stage disease. For patients with stage IB2 onwards, concurrent chemoradiation is currently the standard of care. For locally advanced cervical cancer (stage IB2-IVA), 5-year survival rates vary from 80% for IB, 58% for IIB, 35% for IIIA, 32% for IIIB and 16% for stage IVA disease.[5]

NACT has been used before surgery for early cervical cancer (stage IB-IIA) and also before RT for locally advanced disease (IIB-IVA). This was based on the principle that (i) chemotherapy leads to reduction in size of the primary tumour making subsequent local treatment–RT or surgery more effective; (ii) uncompromised blood flow in RT-naïve patients results in a higher concentration of chemotherapy drug at the tumour site; and (iii) chemotherapy can eradicate micro-metastatic disease. The use of NACT before surgery was based on the observation of presence of residual disease in almost one-third of the patients (IIB-IVA) following sequential NACT and radiotherapy; and this led investigators to hypothesize that surgical removal of the remaining tumour mass (thereby removing resistant clone) may be associated with survival benefit.[6] A number of randomized trials using NACT followed by surgery with or without adjuvant RT have addressed this issue. Most of these studies have used short-course (weekly or 2 weekly) chemotherapy for 4–6 weeks followed by surgery/RT.[4] Many of these studies were done before the era of concurrent CTRT. The present study by Gupta *et al*. fills this void. They did not find any benefit of NACT before surgery; in fact, DFS was inferior compared to the current standard, i.e. concurrent CTRT.

Patients who achieve complete response (CR) to NACT are likely to do better after consolidation with surgery-RT. Lack of survival advantage to NACT in earlier studies has been attributed to lower CR rates, use of two rather than three cycles.[4] Cisplatin is the most active agent against cervical cancer; carboplatin has been used in view of its better toxicity profile. However, a head-to-head comparison of cisplatin with carboplatin in the NACT setting has not been studied. In the present study, the authors chose carboplatin based on an earlier study by the JGOG trial;[7] in this study with non-inferiority design, Kitagawa *et al*. compared paclitaxel and carboplatin to paclitaxel and cisplatin for the treatment of recurrent or metastatic cervical cancer where almost half the patients were previously exposed to cisplatin.[7] The

authors concluded that treatment with paclitaxel and carboplatin was non-inferior to paclitaxel and cisplatin and should be a standard treatment option for metastatic or recurrent cervical cancer. However, cisplatin is still the key drug for patients who have not received platinum agents.[7] The results in the present study are contrary to earlier reports and two meta-analyses.[8,9] Kim *et al*. reviewed data of five randomized trials and four observational studies. NACT, before surgery in patients with stage IB1 to IIA, reduced the need for adjuvant RT therapy by decreasing tumour size and lymph node metastasis and distant metastasis; however, it failed to improve survival compared to patients who underwent primary surgery.[8] Rydzewska *et al*. for Cochrane Database Systematic reviews analysed results of six randomized studies; both OS (HR 0.77, 95% CI 0.62–0.96, p<0.02) and progression-free survival were significantly improved with NACT (HR 0.75, 95% CI 0.61–0.93, p=0.008).[9] Currently, another randomized study similar to the present study is under progress and is being conducted by the European Organization for Research and Treatment of Cancer. Patients with cervical cancer stage IB2, IIA and IIB are being randomized to neoadjuvant cisplatin-based chemotherapy followed by radical hysterectomy versus concurrent CTRT. With the target of 686 patients, the trial is likely to be completed in a year's time.[10] These two studies are expected to confirm the role of NACT before surgery for early cervical cancer. In the present study, 57% of patients belonged to stage IIB and the results were driven by this group translating into better DFS in the CTRT arm.

OS remains the gold standard for outcome assessment and in the present study there was no difference in the OS; however, the study was not planned for OS as an outcome endpoint. The NACT arm was radiotherapy-naïve, had more local recurrences that were salvaged by subsequent RT. For a disease with similar OS in the two treatment arms, estimating the quality of life would help to choose one regimen over another. In addition, for a small number of patients who are young and wish to preserve fertility, NACT followed by surgery might be a reasonable option. Two studies using weekly paclitaxel and carboplatin for 4–6 weeks as dose-dense chemotherapy before radiotherapy have shown encouraging results;[11,12] this is being currently studied in a phase 3, multicentric trial.[13]

Thus, the current management of cervical cancer requires a multidisciplinary team approach. For patients with early disease, the decision to go for upfront surgery or RT or use of neoadjuvant chemotherapy prior to surgery or fertility preservation surgery should be based on a careful review of clinical findings, imaging, pathology and availability of surgical skills so as to allow the patient to make an informed decision toward initial therapy. For patients with locally advanced disease, concurrent CTRT remains the standard approach.[4,14]

Conflicts of interest. None declared

REFERENCES

1 Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. *CA Cancer J Clin* 2016;**66:** 7–30.
2 National Centre for Disease Informatics and Research National Cancer Registry Programme Indian Council of Medical Research: Three-Year Report of Population Based Cancer Registries; 2012–2014. Available at *www.icmr.nic.in/ncrp/pbcr_2012-14/ALL* (accessed on 30 Mar 2018).
3 Small W Jr, Bacon MA, Bajaj A, Chuang LT, Fisher BJ, Harkenrider MM, *et al.* Cervical cancer: A global health crisis. *Cancer* 2017;**123:**2404–12.
4 Kumar L, Gupta S. Integrating chemotherapy in the management of cervical cancer: A critical appraisal. *Oncology* 2016;**91** Suppl 1:8–17.
5 Cervical Cancer Stages—American Cancer Society. Available at *www.cancer.org/cancer/cervical-cancer/detection-diagnosis-staging/staged* (accessed on 30 Mar 2018).
6 Kumar L, Pramanik R, Kumar S, Bhatla N, Malik S. Neoadjuvant chemotherapy in gynaecological cancers—Implications for staging. *Best Pract Res Clin Obstet Gynaecol* 2015;**29:**790–801.
7 Kitagawa R, Katsumata N, Shibata T, Kamura T, Kasamatsu T, Nakanishi T, *et al.* Paclitaxel plus carboplatin versus paclitaxel plus cisplatin in metastatic or recurrent cervical cancer: The open-label randomized phase III trial JCOG0505. *J Clin Oncol* 2015;**33:**2129–35.
8 Kim HS, Sardi JE, Katsumata N, Ryu HS, Nam JH, Chung HH, *et al.* Efficacy of neoadjuvant chemotherapy in patients with FIGO stage IB1 to IIA cervical cancer: An international collaborative meta-analysis. *Eur J Surg Oncol* 2013;**39:**115–24.
9 Rydzewska L, Tierney J, Vale CL, Symonds PR. Neoadjuvant chemotherapy plus surgery versus surgery for cervical cancer. *Cochrane Database Syst Rev* 2012;**12:**CD007406.
10 Chemotherapy Followed By Surgery vs. Clinical Trials. Available at *www.clinicaltrials.gov/ct2/show/NCT00039338* (accessed on 31 Mar 2018).
11 Singh RB, Chander S, Mohanti BK, Pathy S, Kumar S, Bhatla N, *et al.* Neoadjuvant chemotherapy with weekly paclitaxel and carboplatin followed by chemoradiation in locally advanced cervical carcinoma: A pilot study. *Gynecol Oncol* 2013;**129:** 124–8.
12 McCormack M, Kadalayil L, Hackshaw A, Hall-Craggs MA, Symonds RP, Warwick V, *et al.* A phase II study of weekly neoadjuvant chemotherapy followed by radical chemoradiation for locally advanced cervical cancer. *Br J Cancer* 2013;**108:** 2464–9.
13 Interlace A phase III multicentre trial of weekly induction. Available at *www.ctc.ucl.ac.uk/TrialDetails.aspx?Trial=89* (accessed on 22 Jan 2018).
14 Kumar L, Harish P, Malik PS, Khurana S. Chemotherapy and targeted therapy in the management of cervical cancer. *Curr Probl Cancer* 2018. pii: S0147-0272(18) 30019–9.

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