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Editorial Comment

Neoadjuvant chemotherapy for locally advanced cervical cancer

E. Timotheadou*, M.E. Gore

Department of Medicine, Royal Marsden Hospital, London, UK

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The management of patients with locally advanced cancer of the uterine cervix remains a challenge, despite recent encouraging data. Historically, radiotherapy has been the standard treatment, with 5-year survival rates of approximately 40% (range 15–75%), depending on the patient's stage of disease [1–6].

Several randomised trials have evaluated multimodality approaches such as chemoradiation. In recent years, six randomised controlled trials have demonstrated a survival benefit for concurrent chemoradiation over conventional radiotherapy [7–12]. This led to the 1999 National Cancer Institute (NCI) Alert, which strongly advised that chemoradiation should be considered for all patients with cervical cancer requiring radiotherapy. These six trials represented only a sub-set of the published data and were significantly heterogeneous with regard to both the local and systemic treatments delivered and the patient's stage.

A meta-analysis that included 4580 patients from 19 randomised trials [13] added support to those results, which showed that concurrent chemoradiation was superior to radiotherapy alone. Highly significant benefits were demonstrated for both overall and disease-free survival, with absolute improvements of 12% (Hazard Ratio (HR) 0.71, 95% Confidence Interval (CI) 8–16) and 13% (95% CI 13–19, $P=0.0001$), respectively. In addition to the expected gains in local control, a significant reduction in distant relapses was also seen, with both platinum and non-platinum chemotherapies. This was achieved with short courses of chemotherapy in combination with local treatment and the effect was more prominent in trials that included larger numbers of stage I and II patients ($\geqslant 70\%$ versus $\leqslant 70\%$, $P=0.009$).

This unexpected reduction in distant relapse rates has raised the question of whether chemotherapy, in addition to its local radio-sensitising effect, is also active against micrometastatic disease and therefore a neoadjuvant chemotherapy strategy should be explored in this tumour type. The rationale for neoadjuvant chemotherapy is that as well as eradicating micrometastases, it would debulk the tumour and thus improve the outcome of subsequent surgery or radiotherapy. Chemotherapy given to treatment-naïve patients can be more effective in the neoadjuvant as opposed to other settings, partly because it is being delivered in the setting of an uncompromised tumour blood supply and to a population of chemosensitive tumour cells. It could also be less toxic than concurrent chemoradiation.

Neoadjuvant chemotherapy for cervical cancer still remains controversial, despite its long history and the fact that compared with chemotherapy for advanced or metastatic cervical cancer, response rates are much higher in the neoadjuvant setting (range 45–95%) [14–17]. Several randomised phase III studies have failed to demonstrate a survival benefit over conventional radiotherapy alone [18–23] and some trials have even shown a detrimental effect of neoadjuvant chemotherapy compared with radiotherapy [20,22]. A variety of clinical and biological factors may have contributed to this, including chemotherapy-related mortality, poor patient compliance to longer treatment schedules and accelerated repopulation of resistant tumour clones [24,25].

The meta-analysis by Tierney and colleagues published in this current issue of the *European Journal of Cancer* includes 21 randomised trials of neoadjuvant chemotherapy that have been conducted between 1975 and 2000 [26]. Individual patient data (IPD) were collected, validated and re-analysed, in order to investigate in greater detail the possible differences in treatment effects between subgroups of patients and to evaluate long-term toxicity.

Two separate comparisons are presented in this review; the first between neoadjuvant chemotherapy followed by radical radiotherapy versus radical radiotherapy alone and the second between neoadjuvant chemotherapy followed by surgery ($\pm$radiotherapy) versus radical radiotherapy alone.

* Corresponding author.

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There are 2074 patients in the first analysis, with a median follow-up of 5.7 years. Trial heterogeneity was a major setback to the analysis, although some interesting results were obtained, when the trials were grouped together according to cycle duration and dose intensity (DI). Trials where the chemotherapy cycles lasted longer than 14 days had a pooled HR of 1.25, representing a 25% increase in the risk of death ($P=0.005$), while for shorter chemotherapy cycles, the HR was 0.83 and there was a reduction of 17% in the risk of death ($P=0.045$). These results translated into an absolute 8% reduction in 5-year survival (from 45 to 37%) for patients treated with longer cycles, as opposed to a benefit of 7% (from 45 to 52%) for those treated with cycles that lasted shorter than 14 days. A comparison according to DI was made between trials delivering less than 25 mg/m^2/week and those delivering an equal or greater dose. An HR of 1.35 for the lower intensity group indicated an increase of 35% in the risk of death ($P=0.002$), in contrast to an HR of 0.91 ($P=0.2$) and a reduction of 9% in the risk of death for the latter group. The absolute reduction in the 5-year survival for the first group (low DI) was 11% (from 45 to 34%), while in the second (high DI), an increase of 3% (from 45 to 48%) was noted.

The second analysis, between neoadjuvant chemotherapy followed by surgery (±radiotherapy) versus radical radiotherapy, included 872 patients and the main cytotoxic agent used was cisplatin. Analysis for survival significantly favoured neoadjuvant chemotherapy, with an HR of 0.65, a reduction in the risk of death of 35% and an absolute gain of 14% in the 5-year survival ($P=0.0004$).

It is clear that the major difficulty this meta-analysis had to overcome was the heterogeneity between trials. This significantly restricted the comparisons that could be made. No statistically significant difference in survival could be demonstrated between neoadjuvant treatment and conventional radical radiotherapy alone when all trials were analysed together.

Once again, it seems that we have more questions than answers.

When this meta-analysis was planned, radiotherapy was the standard treatment, but in the meantime this has changed to concurrent chemoradiation. Therefore, perhaps the next issue to address is whether neoadjuvant chemotherapy should be given instead of chemoradiation. Published data from two consecutive non-randomised phase II trials suggest that neoadjuvant treatment can be as effective as concurrent chemoradiation [27]. Currently, this question is being investigated by the European Organisation for Research and Treatment of Cancer (EORTC) in a randomised trial (EORTC 55994) that compares neoadjuvant chemotherapy followed by surgery versus concurrent chemoradiation as the standard arm.

Optimising DI and selecting the most efficient cytotoxic combination is another major issue and, as Tierney's analysis shows, this might have a significant impact on the outcome of future clinical trials.

In addition, long-term toxicity is an important issue for survivors, as chronic side-effects like rectal or bladder incontinence and sexual dysfunction can significantly affect quality of life. The lack of sufficient data regarding acute and long-term treatment toxicity is a disappointing feature in this review. However, the authors had little control over this.

A new generation of active chemotherapeutic agents, including taxanes, vinorelbine and gemcitabine are currently being investigated in advanced disease and have produced encouraging response data. Incorporation of these novel agents in future schedules, with or without cisplatin, may offer further opportunities for neoadjuvant strategies. Furthermore, the development of targeted treatments including epidermal growth factor receptor (EGFR) inhibitors, Tyrosine Kinase inhibitors and monoclonal antibodies might provide another option for improving responses, particularly considering their favourable toxicity profiles compared with conventional cytotoxics. It is also possible that these novel agents may be associated with fewer treatment delays, in a setting where these are very likely to have a detrimental effect on treatment outcome.

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