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Editorial

Adjuvant chemotherapy in locally advanced cervical cancer: the ceiling remains unbroken

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▸ See the article "A randomized controlled trial comparing concurrent chemoradiation versus concurrent chemoradiation followed by adjuvant chemotherapy in locally advanced cervical cancer patients: ACTLACC trial" in volume 30, e82.

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The treatment of cervical cancer underwent a major change about two decades ago when a number of phase III clinical trials reported, almost together, significant improvements in survival outcomes with addition of concomitant chemotherapy to definitive radiotherapy [1]. Concomitant chemoradiation, using cisplatin-based regimens, mostly single agent weekly cisplatin, has been the standard of care for locally advanced cervical cancer since then. However, a substantial minority of patients continue to relapse and die of their disease despite receiving optimal chemoradiation treatment. There have been numerous attempts, some ongoing, to improve the outcomes with various therapeutic strategies, including neoadjuvant chemotherapy followed by surgery [2,3], neoadjuvant chemotherapy followed by concomitant chemoradiation (ClinicalTrials.gov identifier: NCT01566240), adjuvant chemotherapy after chemoradiation [4-6], and, more recently, use of immunotherapeutic approaches [7]. However, no therapeutic strategy has clearly and unequivocally improved the outcomes in locally advanced cervical cancer beyond those achieved with concomitant chemoradiation. The report in this issue of the Journal by Tangjitgamol et al. [8], is one more laudable, but failed attempt.

Tangjitgamol et al. [8] have reported a randomized controlled trial which compared the outcomes achieved with standard concomitant chemoradiation versus those achieved with addition of 3 cycles of paclitaxel and carboplatin to concomitant chemoradiation, in patients with stages IIB to IVA cervical cancer. Notable features of the study population include exclusion of patients with paraaortic lymph nodes, approximately three-fourths of patients having squamous cell carcinoma, more than 95% patients having stage IIB or IIIB cancer and an imbalance between concomitant chemoradiation arm (20.9%) and adjuvant chemotherapy arm (26.9%) with respect to radiologically detected pelvic lymph nodes. Also of note, only approximately two-thirds of patients in the adjuvant chemotherapy arm actually completed the planned 3 cycles of paclitaxel and carboplatin. From the design and conduct perspective, an interim analysis was planned with predefined futility and overwhelming efficacy limits, but undefined alpha spending plan. As it turned out, the trial was stopped early because of futility when it had accrued 54.2% of its planned sample size (500). The latter itself was based on a somewhat optimistic assumption of improvement in 3-year progression-free survival (PFS) by 15 percentage points in the experimental arm over

a control arm PFS of 55%. The main result of the study was lack of significant improvement in PFS and overall survival (OS) with the addition of adjuvant chemotherapy to concomitant chemoradiation, at a relatively short median follow-up of 27.4 months. Severe grades (3–4) of neutropenia, thrombocytopenia and several non-hematological toxicities (gastrointestinal, genitourinary, and neurological) were numerically higher in the adjuvant chemotherapy arm.

Several important points need to be considered while appraising the results of this study. First, there is always an element of uncertainty when a study is terminated earlier than planned, affecting both its power and precision of the results. This is especially relevant to this study wherein only a little more than half the planned sample size and an unreported fraction of planned events were actually accrued. The OS in concomitant chemoradiation arm of this study has been reported to be 80.1%, a figure which is higher than most other studies in patients with stage IIB or IIIB disease. This additionally indicates premature analysis of data at a relatively short follow-up before sufficient events have occurred. Second, cervical cancer literature is replete with studies that report and compare time-to-event outcomes, like loco-regional and distant recurrences, as simple proportions. It is also worth noting that these outcomes are captured only as 'first events' in most study protocols and more than 1 outcome (in this example local and distant recurrence) 'compete' to be the first event, often resulting in imbalanced censoring between the study groups. Thus, it may not be appropriate to draw conclusions about the effect of adjuvant chemotherapy on the pattern of recurrence from this study. Third, it is unlikely that choice of carboplatin instead of cisplatin as part of the adjuvant chemotherapy regimen impacted the outcome. The primary result of a Japanese randomized study in recurrent or metastatic setting showed that paclitaxel and carboplatin was non-inferior to paclitaxel and cisplatin [9]. In the neoadjuvant setting, the results of 2 large and similarly designed trials suggest that both paclitaxel plus carboplatin [2] and cisplatin-based regimens [3], prior to surgery, produce similar results, and fail to improve outcomes compared to standard chemoradiation. Biologically, it is likely that tumor clones that are resistant to cisplatin plus radiotherapy, and survive this treatment, are also resistant to further adjuvant platinum-based chemotherapy. Thus, it is also unlikely that extending the adjuvant regimen for a few more cycles or modifying the cycle duration (4 weeks in this study) would have altered the efficacy outcomes. The results of OUTBACK (ClinicalTrials.gov identifier: NCT01414608) and INTERLACE (ClinicalTrials.gov identifier: NCT01566240) trials that are testing, respectively, adjuvant and neoadjuvant taxane-platinum chemotherapy added to concomitant chemoradiation, will provide further evidence for the chemotherapy question.

The strength of this study is the multicenter participation with reasonably quick patient accrual. This is likely to have created and enabled a framework that could be used to conduct other locally relevant clinical trials in this population.

Where do we go from here? In the larger context, the incidence of cervical cancer is declining in many hitherto high incidence regions and it is likely that locally advanced disease will also decline. The importance of feasible and implementable screening strategies [10] cannot be overemphasised. From a public health perspective, enabling the delivery of high-quality radiotherapy, including brachytherapy, in underserved regions of the world, which also have the highest incidence of advanced cervical cancer, is of paramount importance. We also hope that new, potentially non-cross resistant treatments, such as immune checkpoint inhibitors, will improve the outcomes in locally advanced disease. However, even if successful, it is unclear whether such expensive treatments will be feasible in populations where they are most required.

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In summary, cisplatin based concomitant chemoradiation continues to remain the standard of care in patients with locally advanced cervical cancer.

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