

Radiotherapy treatment strategies for squamous cell carcinoma of the cervical oesophagus: moving toward better outcomes

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Squamous cell carcinoma of the cervical oesophagus (CEC) is a rare disease (1). In adjunct, most of the prospective randomized trials, investigating combined chemo-radiation for oesophageal cancer, marginally enrolled (or excluded at all) patients with cervical localizations (2). Hence, reliable and robust clinical data in this setting are still lacking, especially because of the retrospective frame of most of the studies which employed different radiation and chemotherapy schemes (3). Similarly, in surgical series, where disease has often borderline presentation with that of laryngo-hypopharyngeal cancer and patients are frequently treated with total laryngo-pharyngectomy, neck dissection and partial or total esophagectomy, it is hard to assess clinical outcomes for pure disease of the CEC (1). As a result, evidence-based clinical decision-making needs to be improved in this oncological scenario (4). The study by McDowell *et al.* from the Princess Margaret Hospital in Canada, attempted at providing a glimpse on the impact of different radiotherapy (RT) strategies on CEC patients treated with definitive chemo-radiation (5). Both RT (total dose and delivery technique) and chemotherapy (regimens) variables were explored. Specifically, three protocols were investigated over 17 years [1997–2003] on 81 patients. Two-dimensional RT (2DRT), delivered with a hypofractionated schedule (54 Gy in 20 fractions) concomitant to 5-fluorouracil (5-FU)

and either mitomycin-C (MMC) or cisplatin (DDP) was compared in terms of overall survival (OS) to 3-dimensional RT (3DCRT) up to a conventionally fractionated total dose >60 Gy associated to elective nodal irradiation (ENI) and concurrent DDP and to >60 Gy intensity modulated RT (IMRT), delivered with conventional fractionation, associated to ENI and concomitant DDP (5). Multivariable analysis, after adjustment for age and chemotherapy, showed a significantly improved OS for patients treated with IMRT compared to those treated with 2DRT [hazard ratio (HR): 0.4; 95% confidence interval (CI): 0.2–0.8; P=0.005] and a trend for OS improvement for IMRT compared to 3DCRT (HR: 0.6; 95% CI: 0.3–1.0; P=0.061). No significant difference was found between 2DRT and 3DCRT (P=0.29). Overall, the IMRT group showed a significantly higher OS compared to non-IMRT strategies (HR: 0.57; 95% CI: 0.3–0.8; P=0.008) and a higher delivered dose was found to have borderline significant correlation to OS (HR: 0.97; 95% CI: 0.95–1.00; P=0.075) (5). The study by McDowell *et al.* (5) gives interesting food for thoughts. At first, prognosis for CEC patients can be generally regarded as dismal. Two-year OS on the whole cohort was 45% (95% CI: 36–58%), ranging from 33% (2DRT group) to 53% (IMRT group). Of course, this can be partially due to the high rate

of risk factors and comorbidities that this subset of patients usually has (smoking, alcohol, cardiovascular disorders, second cancers). Nevertheless CEC-related deaths account for a substantial part of the mortality rate, since the rate of deaths related to causes other than cancer was on average around 26%. Moreover, 2-year loco-regional and distant control were only 58% (95% CI: 45–67%; 43% for 2DRT and 68% for IMRT) and 61% (95% CI: 51–72%; 62% for 2DRT and 59% for IMRT), respectively. If we take a look at the pattern of failure, among 55 relapses at any site, 34 were local and 16 were regional. So, a substantial amount of cancer-related mortality is due to loco-regional failures in this setting and hence there is still room for improving locoregional control. Secondly, it is clear that technological improvements have led part of the survival benefit that RT has been able to provide to cancer patients in recent years (6). IMRT and image-guided RT are able to deliver RT treatments with robust conformality, abrupt dose fall off and reliable accuracy (7). This allows offering patients dose-escalated treatment regimens with a more favourable toxicity profile, optimizing the therapeutic window with better tumor control and lower normal tissue complication probabilities. In the study by McDowell *et al.*, patients in the IMRT group were given 70 Gy in 35 fractions to the macroscopic primary tumor and nodal disease and 50 Gy in 25 fractions to the prophylactic nodal volumes (superior mediastinal, bilateral supraclavicular and level III and IV neck lymph nodes) (5). Concurrent DDP at 100 mg/m² (weeks 1, 4, 7) was administered. Such an intense treatment regimen can only be given if highly-conformal delivery techniques (such as IMRT) are employed to decrease the toxicity profile of dose-dense combination therapy. Third, McDowell *et al.* (5) reported a non-statistically significant trend in favor of IMRT *vs.* non-IMRT techniques in terms of less significant late swallowing difficulties (57% *vs.* 80%), defined as percutaneous endoscopic gastrostomy (PEG) dependence or oesophageal stenosis requiring dilatation. These data suggests a better compliance to treatment in spite of the higher doses delivered. The series by McDowell has intrinsic limitations, mainly due to the retrospective nature of the study and the large timespan of enrollment determining potential selection biases related to patient, tumor and treatment features. Nevertheless, it gives an important suggestion about the benefit in terms of survival when employing highly conformal dose-escalated

RT and ENI (delivered with IMRT) in association to concurrent DDP compared to conventional techniques for CEC patients. Yet, advances in early diagnosis and mindful integration of RT with chemotherapy (including novel agents) and radical surgery remain strongly demanded to substantially improve clinical results in this subset of patients, which remain poor in general (8,9).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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