Absent benefit of accelerated concomitant chemoradiotherapy

We read with interest the report of the GORTEC 99-02 randomised phase 3 trial[1] in locally advanced head and neck carcinoma that compared altered fractionation schedules with or without chemotherapy with conventional concomitant chemoradiotherapy. The idea behind accelerated radiotherapy is that a shortened overall treatment time will reduce tumour-cell repopulation during treatment.[2] A meta-analysis showed a small survival benefit of 3·4% at 5 years for altered fractionation radiotherapy in the absence of chemotherapy.[3] Before the GORTEC 99-02 and RTOG 0219 studies,[4] whether the combination of acceleration and concomitant chemotherapy is beneficial compared with conventionally fractionated chemoradiotherapy was uncertain.

The GORTEC study[1] compared conventionally fractionated chemoradiotherapy (70 Gy in 35 fractions over 7 weeks plus three cycles of 4-day concomitant carboplatin-fluorouracil) with accelerated radiochemotherapy (70 Gy in 6 weeks plus two cycles of 5-day concomitant carboplatin-fluorouracil) and very accelerated radiotherapy (64·8 Gy in 3·5 weeks with 1·5 Gy fractions twice daily). The two concomitant chemoradiotherapy groups had equivalent outcomes whereas accelerated radiotherapy was inferior. These results are consistent with the RTOG 0129 study,[4] which showed no benefit of an accelerated schedule of 72 Gy in 6 weeks with two cycles of concomitant cisplatin versus a conventional group of 70 Gy in 7 weeks with three cycles of cisplatin. Therefore, accelerated radiotherapy does not seem beneficial when combined with concomitant chemotherapy.

Jean Bourhis and colleagues[1] note that in the GORTEC study the conventional chemoradiotherapy group received 17% more chemotherapy than did the accelerated radiochemotherapy group, and explain their findings by concluding that "acceleration of radiotherapy cannot fully compensate for a missed dose of chemotherapy". However, an alternative explanation is that use of concomitant chemotherapy minimises tumour-cell repopulation and hence precludes any benefit of radiotherapy acceleration. The explanation is especially important in view of the increasing use of modestly accelerated chemoradiotherapy with—by contrast with the GORTEC study—a reduced total radiotherapy dose.[2] If this alternative explanation is correct, acceleration would be inadequate to compensate for a reduction in radiotherapy dose.

We note that compliance with the third cycle of chemotherapy in the conventionally fractionated chemoradiotherapy group of the GORTEC study was poor (given to 203 of 279 patients). We would be interested to learn whether there is any correlation between chemotherapy delivery (two or three cycles in the conventional chemoradiotherapy group) and outcome to support the authors' conclusion with regard to the importance of chemotherapy dose intensity and the absent benefit of acceleration.

We declare that we have no conflicts of interest.

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1 Bourhis J, Sire C, Graff P, et al. Concomitant chemoradiotherapy versus acceleration of radiotherapy with or without concomitant chemotherapy in locally advanced head and neck carcinoma (GORTEC 99-02): an open-label phase 3 randomised trial. *Lancet Oncol* 2012; **13:** 145–53.

2 Orlandi E, Palazzi M, Pignoli E, Fallai C, Giostra A, Olmi P. Radiobiological basis and clinical results of the simultaneous integrated boost (SIB) in intensity modulated radiotherapy (IMRT) for head and neck cancer: a review. *Crit Rev Oncol Hematol* 2010; **73:** 111–25.

3 Bourhis J, Overgaard J, Audry H, et al. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet* 2006; **368:** 843–54.

4 Ang KK, Harris J, Wheeler R, et al. Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 2010; **363:** 24–35.

Authors' reply

We thank Prestwich and Sen for their comments about the report of our GORTEC 99-02 trial.[1] The results of this randomised trial did not show a benefit of acceleration of radiotherapy when combined with concurrent chemotherapy. We agree that this finding could be due to several factors, including the possibility that chemotherapy could minimise tumour-cell repopulation during radiotherapy and limit the benefit of acceleration.

With regard to the potential correlation between the dose intensity of chemotherapy and clinical outcome in the conventional chemoradiotherapy group, we noted a non-significant trend towards more distant metastases, decreased progression-free survival, and worse survival with two cycles versus three (table, appendix). However, this analysis should be interpreted with caution because it is potentially biased. We did not decide what number of chemotherapy cycles to give (ie, two *vs* three) at the beginning of the treatment; rather several factors (eg, toxic effects or performance status impairment) meant that some patients could not receive the third cycle. Thus, unlike randomised trials, the groups defined by the number of cycles received could be unbalanced for

See Online for appendix

	HR (95% CI)	p
Progression-free survival	1·438 (0·997–2·074)	0·0518
Overall survival	1·402 (0·965–2·037)	0·0764
Locoregional failures	1·521 (0·923–2·508)	0·0998
Distant metastases	1·822 (0·999–3·321)	0·0503

HR and p values were calculated after adjustment for tumour stage, node stage, tumour site, and age. HR=hazard ratio.

Table: **Hazard ratios for progression-free and overall survival, locoregional failure, and distant metastases of patients given two chemotherapy cycles (n=55) compared with those given three chemotherapy cycles (n=190) in the conventional chemoradiotherapy group**