stage III-IV head and neck cancer except in N0 patients where loco-regional control was significantly improved.

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Erythropoietin improves the oxygen carrying capacity of mouse blood without changing hypoxia in a murine tumour model

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Background: It has been suggested that by increasing the haemoglobin content of blood one should be able to increase its oxygen carrying capacity and thereby decrease tumour hypoxia. The aim of this pre-clinical study was to investigate the ability of erythropoietin (EPO) to achieve this.

Material and methods: A C3H mammary carcinoma grown in the right rear foot of female CDF1 mice was used when at 200 mm^3 in size (the radiobiological hypoxic fraction is 10-15% at this size). EPO (2000 U/ml; Janssen-Cilag) was dissolved in saline and different concentrations injected intraperitoneally 3 times/week at 0.02 ml/g body weight. Single blood samples (80 ul) were taken from the suborbital sinus of mice and analysed using an ABL300 Acid-Base Laboratory and OSM Hemoximeter, and haematocrit levels determined on an Adams haematocrit reader. Tumour oxygen partial pressure distributions were obtained using an Eppendorf oxygen electrode. Radiation (240 kV x-rays) was locally administered to tumours using a fractionated schedule of 10 fractions in 2 weeks (4 Gy/day) followed by graded top-up doses and response assessed by calculating the percentage of animals showing local tumour control 90 days later. Following logit analysis the TCD50 value (radiation dose producing tumour control in 50% of treated animals) was calculated. When combined with EPO the radiation and EPO treatments were started at the same time.

Results: In untreated animals the mean (± 1 S.E.) haematocrit level and oxygen carrying capacity of mouse blood was 49% (± 0.5) and 9.0 mmol/L (± 0.2), respectively. Injecting EPO caused a gradual increase in haematocrit reaching a plateau within 2-3 weeks. The haematocrit concentration and oxygen carrying capacity at the time of this plateau were EPO dose dependent, being 56% (± 0.3), 62% (± 0.5) and 67% (± 0.3), and 10.6 mmol/L (± 0.2), 11.7 mmol/L (± 0.1) and 12.3 mmol/L (± 0.1), with EPO doses of 200, 400 and 800 U/ml, respectively. However, there was no change in tumour oxygenation with any of these EPO doses. Nor was the radiation response altered; the TCD50 values (± 95% confidence limits) were 85 Gy (81-89) for animals given radiation alone and 84 Gy (80-87) for those that received concomitant EPO (600 U/ml) and radiation.

Conclusions: EPO improved haematocrit and the oxygen carrying capacity of mouse blood in a dose dependent fashion, but since it had no influence on tumour oxygenation status or radiation response, EPO may not be the answer to the hypoxia problem.

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Recurrences after parotid-sparing radiotherapy

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Purpose: Evaluation of loco-regional failure patterns and survival after parotid-sparing three-dimensional conformal and intensity modulated radiotherapy (IMRT) for head and neck cancer.

Methods and materials: From June 1999 until July 2002, seventy-two selected patients with head and neck cancer were irradiated using a parotid-sparing technique. Three-dimensional conformal planning was used in sixty-eight patients, four patients were treated by IMRT. In all patients the junctional (or high level II) nodes contra-lateral to the tumor were omitted from the clinical target volume to spare the adjacent parotid. All patients presenting with persistent or recurrent loco-regional disease had the radiological image of the failure transposed to the pre-treatment computed tomography used for treatment planning. Minimum, mean and maximal doses administered at the level of the failure were calculated, dose-volume histograms were computed for each failure. The failures were defined to be in- field, marginal misses or out-field depending on the percentage of their volume respectively $\geq$ 95%, between 20% - 95% and $<$ 20%- receiving 95% of the prescribed dose. The rates of 2-year loco-regional control and overall survival were calculated using the Kaplan-Meier method.

Results: The median follow-up was 19 months (range 10-30 months). Both loco-regional control and overall survival rates at 2 year were 67.4%. At the time of analysis, twenty of the seventy-two patients developed a loco-regional failure. Two of these patients (2/20) presented with distant metastasis in combination with a loco-regional relapse. Fifteen of the twenty failures (15/20) occurred within the high dose region, five patients (5/20) developed marginal misses. When reviewing these marginal misses by means of beams-eye-views, in all cases the center of the recurrence was located in the high dose region. No relapses were seen out field and no patients relapsed in the spared junctional area contra-lateral to the tumor.

Conclusion: Parotid sparing radiotherapy, by omitting from irradiation the junctional nodes contra-lateral to the tumor, proved to be safe in our selected patients, since no recurrences developed in that area. As this parotid sparing technique reduces significantly the dose to the parotid contralateral to the tumor and is easy to perform, it should be considered for all such patients.

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Final results of a randomized fractionation trial on radiotherapy for neuropathic bone pain (Trans-Tasman Radiation Oncology Group, TROG 96.05)

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Background: Although there is little evidence for a radiotherapy (RT) dose-response above a single 8 Gy fraction for uncomplicated metastatic bone pain, there have been no prospective studies on bone pain where there is a neuropathic component. The Trans-Tasman Radiation Oncology Group therefore undertook a randomized trial comparing a single 8 Gy (arm 1) with 20 Gy in 5 fractions (arm 2) for this type of pain.

Materials and Methods: Eligible patients had plain x-ray or bone scan evidence of skeletal metastases from a known malignancy with no other metastases along the distribution of the neuropathic pain, and no change in systemic treatment within 6 weeks before RT or anticipated within 4 weeks after RT. This was an "equivalence" trial, the purpose being to determine whether arm 1 was as effective as arm 2. The primary end points were response within 2 months of commencing RT and time to treatment failure. The accrual target was 270 patients (pts).

Results: Between February 1996 and December 2003, 272 pts were randomised from 15 centres (11 Australian, 3 New Zealand, 1 UK). 253 pts satisfied the eligibility criteria (arm 1:2 = 128:125). The commonest primary sites were lung (32%), prostate (28%) and breast (8%); 73% were male; median age was 67 (range 29-89); index sites were spine (88%), rib (10%), other (2%).

The only grade 3 acute RTOG toxicities were (arm 1:arm 2) upper GI tract 1:2 and lung 1:1. In addition, severe but temporary pain "flare" was observed in 7:2 pts. No grade 4 toxicities were reported. There were no statistically significant differences between the treatment arms in development of cord/cauda equina compression or pathological fracture at the index site. On an intention-to-treat basis, the overall response rate was 58% (95% CI = 51-64%) with 26% achieving a complete response. Estimated median time to treatment failure was 3.1 months (95% CI 2.6-3.7 months), and estimated median survival 4.8 months (95% CI 4.0-5.8 months).

Conclusion: Overall, about 3 in 5 patients with neuropathic bone pain responded to RT for a significant proportion of their remaining life span. The results by treatment arm will be presented at the meeting.