Vascularity was assessed as intratumour microvessel density (IMD) within "hot-spots" and intercapillary distance (ICD) for the whole tumour section.

Results: For the 23 parallel measurements there was a significant inverse correlation between the level of tumour oxygenation (% of values < 5 mmHg) and the SI-I ($r = -0.56$, $p = 0.005$) but not rate of uptake. The level of tumour oxygenation also correlated with tumour vascularity measured as ICD ($r = 0.60$, $p < 0.005$) but not angiogenesis measured as IMD ($r = 0.07$, $p = 0.66$). However, there was no significant correlation between MR perfusion parameters and either IMD ($r = 0.07$, $p = 0.81$) or ICD ($r = -0.24$, $p = 0.39$). Maximum tumour diameter at the time of measurement also significantly correlated with SI-I and the level of tumour oxygenation ($r = -0.65$, $p = 0.001$ and $r = 0.36$, $p = 0.043$ respectively).

Conclusion: The results indicate that MR perfusion imaging may be used to give an indication of the level of tumour oxygenation but not angiogenesis (assessed as IMD in biopsy sections) in cervix tumours. More detailed analysis of the MR perfusion time-intensity curves may produce a stronger correlation with tumour oxygenation thus identifying a relatively simple, non invasive method for selecting patients who might benefit from hypoxic modification.

686 ORAL

Differences in palliative radiotherapy practice within Western European countries

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Purpose: To document variations in palliative radiotherapy practice in different types and sizes of radiotherapy departments, within and across Western European countries, and to analyse the possible impact of health care reimbursement systems.

Materials and Methods: A questionnaire was sent to 565 radiotherapy centres in 19 Western European countries, registered in the ESTRO directory of 1997. Palliative radiotherapy practice in terms of total dose, fractionation and treatment complexity was assessed as well as the local reimbursement modalities.

Results: 198 centres (35%) responded. 30 Gy in 3 Gy fractions is the most frequent fractionation schedule (44%), single fractions and 2 Gy fractions being used in res. 13% and 10% of the centres. The majority of the departments uses shielding blocks and performs isodose calculations in less than 50% of patients (res. 79% and 88%). A positive correlation was found ($p = 0.001$) between the size of the department and the fractionation and complexity of the treatment, larger centres favouring shorter and less complex treatments. The same was found for university centres and fractionation ($p = 0.022$), but not for treatment complexity ($p = 0.378$ and 0.440). Both large and university hospitals show a higher proportion of reimbursement through budget and case payment than through fee-for-service ($p = 0.001$ and $p = 0.001$). Fee-for-service represents an incentive towards more fractions ($p = 0.18$) and more complex treatments ($p = 0.001$ and 0.045). National differences in reimbursement systems are thus reflected in the variations in palliative radiotherapy practice.

Conclusion: Besides factors as clinical evidence and local custom, the nature of the reimbursement system also plays a role in the choice of palliative radiotherapy.

687 ORAL

Oesophageal radiotherapy: Potential for dose escalation by conformal techniques

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Purpose: To evaluate the reduction in radiation dose to normal thoracic structures through the use of three-dimensional conformal radiotherapy techniques in the treatment of oesophageal cancer, and to quantify the potential for dose escalation.

Methods: Four different CT-derived treatment plans were created and compared for each of ten patients. A two-phase treatment with conventional straight-edged fields and standard blocks (CV2), a single-phase conformal plan (CF1), a two-phase conformal plan (CF2), and a three-phase conformal plan where the third phase was delivered to the gross tumour only (CF3), were considered for each patient. Treatment plans were assessed using dose-volume histograms and normal tissue complication probabilities (NTCPs) for lung. Escalated dose levels were determined, which would increase tumour control probability (TCP) without increasing the mean lung dose.

Results: Technique CF2 reduced the volume of lung irradiated from 19.7 ± 11.8% (1 SD) to 17.4 ± 12.2% ($p = 0.009$), and reduced NTCP from 2.4 ± 4.0% to 0.7 ± 1.6% ($p = 0.02$). For 48 Gy spinal cord tolerance, technique CF2 permitted a target dose of 60.5 ± 2.1 Gy and technique CF3 a prescribed dose of 63.0 ± 2.9 Gy to the target. Technique CF3 increased TCP from 53.1 ± 5.5% to 78.0 ± 3.2%.

Conclusion: Conformal radiotherapy techniques offer the potential for dose-escalation, and could increase local tumour control substantially without imposing increased lung dose.

688 POSTER DISCUSSION

The links between hypoxia, DNA repair, ATP and radiosensitivity: Time for a paradigm shift

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Classical radiobiology and the linear quadratic (LQ) model cannot explain the common clinical experience that approximately 50% of primary solid tumours can be cured with 60–70 Gy, a dose that only causes moderate damage to normal tissue in 5% of patients. Most normal tissues can tolerate only 4–5 decades of cell kill whereas 8–9 decades are needed to eradicate the last clonogenic cell in a tumour. There is no evidence from in vitro studies that all tumour cells are intrinsically more radiosensitive than all normal cells.

We will provide a new and plausible explanation for this anomaly, using the inducible repair variant of the LQ equation. A computer simulation is used to incorporate data showing a major difference in the effect of acute and chronic hypoxia. This is linked mathematically to recent in vitro data showing that the clonogenic survival after 2 Gy (SF2) is directly proportional to the magnitude of cellular capacity for inducible repair (IRR).

Acute hypoxia leads to an increase in radioresistance by a factor of 3. By contrast, prolonged or chronic hypoxia, with or without glucose depletion, leads to sensitisation by causing a loss of the DNA repair capability. This is accompanied by a fall in the levels of cellular ATP. Thus, two opposing effects of hypoxia have been shown. It is pertinent to ask the magnitude of these 2 effects, which of them occurs in human tumours, and whether the two types of hypoxia can be distinguished.

The biochemical loss of the inducible repair ratio (IRR) is potentially much greater than the chemical protection factor of 3. IRR values range from 1 to 25, and are directly linked to intrinsic oxic radiosensitivity (SF2). Intrinsically resistant cells should therefore be most sensitised by chronic hypoxia/ATP depletion. Even after taking account of the chemical protection factor of 3, the chronically hypoxic cells can be up to 8 times more sensitive than well oxygenated cells. We predict they may actually be the reason why tumours can be cured. This represents a complete paradigm shift.

Our quantitative simulations show that a therapeutic window can never be predicted by the simple LQ model, if we assume that all hypoxic cells are equally resistant. We show however, that using the LQ/IR variant, the clinical observation can be matched if all cells are relatively resistant (the SF2 is about 0.8) and the chronically hypoxic fraction is about 50%.

Current predictive assays for SF2 and hypoxic fraction do not distinguish betwen acute and chronic hypoxia, nor do they take account of the link between the SF2 and IRR values. Predictive tests have shown a wide range in radiosensitivities in both malignant and normal cells, from 0.1–0.9. This relates to clinical radiosensitivity in rank order, but gives rise to unreasonable predictions using the LQ model. Doses of 20 to 400 Gy (in 2 Gy fractions) should be needed to eliminate 9 decades of cells for these SF2 values. In practice all these tumour types show some fraction of cures with doses of 60–70 Gy.

The anomaly between classical radiobiology and clinical knowledge can be explained by the new LQ/IR model if acute and chronic hypoxia are considered separately and SF2 is directly linked to the loss of repair capacity in chronic hypoxia. The use of phosphorus NMR to monitor energy charge depletion via ATP and PI may be a better predictor of clinical outcome than either SF2 assays or hypoxic fraction. estimates.