total irradiated volume and percent lung receiving 20 Gy (V20) for the 2 plans were compared.

Results: Incorporation of PET data into planning resulted in 1.2-5.5 increase in GTV for 11 patients, and 0.5 decrease for 1 patient, allowing differentiation between tumor and atalectasis. Unsuspected mediastinal disease was identified in 4(30%). Radiation ports were altered to provide more adequate coverage of the bioanatomic tumor volume in 8 patients. Despite the mean GTV was 2.8 times greater using PET, average increases in total volume irradiated and V20 were only 30% and 20%. Radiation ports were not changed in 2 patients, and were reduced in 2 patients resulting in 17 to 34% decrease in volume irradiated and V20.

Conclusions: Co-registration of PET with planning CT images provides a bioanatomic target that improves delineation of the tumor by better defining extent of local disease and including positive lymph nodes that may not be apparent using CT alone. Incorporation of PET images into treatment planning reduces the likelihood of geographical misses, which may result in improved local control and survival. This information can further assist 3D treatment planning to customize conformal fields so a greater extent of disease can be treated while minimizing the total volume irradiated and V20, and reducing the risk of toxicity.

960 POSTER DISCUSSION

Target volume definition in non-small cell lung cancer using 3-dimensional image registration of pre- and post-chemotherapy CT scans

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Aim: Inter-clinician variations in delineating target volumes are a source of systematic errors in radiotherapy treatment planning (RTP). We compared the results of visual transfer of contours to RTP scans with transfer after 3D image registration, in patients receiving induction chemotherapy for non-small cell lung cancer (NSCLC).

Materials and methods: Pre-chemotherapy diagnostic CT scans (on a curved couch-top) and RTP scans (hard couch-top and arm-rest) were performed in 5 patients who received induction chemotherapy, followed by 'involved-field' radiotherapy. A second RTP scan was performed after chemotherapy, and pre-chemotherapy gross tumor volumes (GTV) were reconstructed at an ACQSIMTM workstation by 3 clinicians in the following manner: (i) a 'GTV-visual' generated while viewing the hard copies of the diagnostic CT scan, (ii) a 'GTV-match' after on-screen registration of pre- and post-chemotherapy RTP scans and (iii) GTV's after registration of the pre-treatment diagnostic CT scans with the post-chemotherapy RTP scan. Image registration was performed using the contoured body of a thoracic vertebra adjacent to the tumor. The 'GTV-match' was used for the actual treatment planning. Data were analysed using Cadplan and reproducibility of the contoured GTV's was defined by the ratios of common areas of overlap for the respective contours.

Results: The best method of image registration, as assessed both by clinicians and by ACQSIMTM software was achieved using pre-chemotherapy RTP scans. GTV's derived with 3D image registration were almost invariably larger than those derived using visual contouring (57.4±10% versus 70.8±7%, mean±1SD). Similarly, the mean reproducibility of contouring per patient improved from 61±15.6% to 71.7±9.4% with 3D registration.

Conclusions: 3D image registration of pre- and post-chemotherapy RTP scans resulted in the generation of larger, and more reproducible, GTV's than that derived using visual matching. This technique may be even more important for highly chemosensitive tumors such as small cell lung cancer. The resulting improvement in target volume coverage is likely to improve local tumor control.

961 POSTER DISCUSSION

Preservation of salivary function by IMRT: importance of PTV-CTV margin

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Purpose: Xerostomia has a major impact on quality of life after radiotherapy for head and neck tumours. We investigated to what extent the size of the margin between CTV (clinical target volume) and PTV (planning target volume) influences the prospects of modulating the intensity of the beam (IMRT) to preserve parotid gland function.

Methods: For definition of CTV we used a planning CT-scan in a patient treated with primary radiotherapy for oropharyngeal cancer (T2N0). We delineated the CTV for the primary tumour (gross target volume + 1 cm margin for microscopic disease) and the regional node levels II-IV bilaterally. We developed a class solution using IMRT (ITP, PLATO) inverse planning, with 7 beams and 15 intensity levels per beam. The NTCP (normal tissue complication probability) for <25% of the initial parotid gland function was calculated, using IMRT plans, with a margin between CTV and PTV in a range of 0-10 mm. NTCP values of parotid function were derived from our detailed parotid salivary flow measurements in 108 patients treated for head and neck malignancies.

Results: The NTCP for contralateral parotid function was <10% for a PTV-CTV margin of 6 mm or less, 25% for a margin of 8 mm, and 31% for a margin of 10 mm. The NTCP for ipsilateral parotid function was 20% for a margin of 4 mm or less, 31%, 38% and 65% for a margin of 6, 8, and 10 mm, resp.

Conclusion: The uncertainty margin between CTV and PTV, necessary for setup-errors and movement of the patient in the mould, is crucial for the prospects of IMRT to preserve parotid function. Measurements should be taken to keep the margin within 6 mm.

962 POSTER DISCUSSION

ESTRO/ASTRO consensus statement on the measurement of metastatic bone pain in radiotherapy trials

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Background: A total of 11 randomised phase III trials, each involving over 100 patients, have addressed the question of optimal fractionation for the treatment of metastatic bone pain. Review of these trials has shown wide variation in the methods used to measure bone pain. The impact of this is highlighted in the analysis of the Dutch bone pain trial reporting a complete response rate of 25% with a pain score of zero, 12% when analgesic use is included and only 4% if global quality of life is used. Across studies wide variation is also seen with the additional impact of differing patient populations

Method: A consensus initiative was established under the auspices of ESTRO and ASTRO in July 2000 to evaluate the various endpoints used and establish a consensus position for definition of pain scoring in future trials of palliative radiotherapy. The first round of discussions held at ASTRO 2000 was based on a questionnaire completed by 35 prominent investigators in the field of metastatic bone pain.

Results: This showed that in some areas of pain assessment there was a clear majority consensus, for example in the use of patient rather than physician scores, the use of a 10 point categorical scale and the use of analgesics as at least a secondary end-point. Other areas identified wider variation and uncertainty, for example definition of partial response, the most appropriate pain to measure, analgesic scoring and impact of retreatment. A second round questionnaire is underway addressing more specific issues within these uncertain areas on the basis of which a consensus statement will be formulated for presentation and approval at the annual ESTRO and ASTRO meetings in Autumn 2001.

Gynaecological cancer

963 POSTER DISCUSSION

Retrospective study of the impact of taxol/platinum (TAX-P) vs non-taxol/platinum (NOTAX-P)chemotherapy on response and survival of patients with advanced ovarian cancer (AOC). Report from a single institution

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Objective: To evaluate if taxol-platinum chemotherapy has improved the outcome of patients (p) with AOC treated in a single institution.

Patients and Methods: Retrospective study. From 1986 to 2000, 190 pt with AOC received platinum-based chemotherapy (64.7% NOTAX-P, 35.3% TAX-P). Characteristics of the p were (NOTAX-P vs TAX-P): mean age: 56 vs 58 y, at least surgical biopsy: 85% vs 82%, FIGO III/IV stages: 79%/21% vs 77%/23%, residual disease >2 cm: 84% vs 80%, 2nd laparotomy: 42%

vs 46%. There were not differences between both groups in % of patients who received consolidation therapy or in the best response to salvage regimens.

Results: (NOTAX-P vs TAX-P): Clinical response rates were complete (CCR): 38.2% vs 50%, partial (CPR): 17.1% vs 26% and overall (OCR): 55.3% vs 76%. The 95% CI values for the difference in response were for CCR: -4 to 27% and for OCR: 6 - 35% in favour of TAX-P. In 68 p with CCR or CPR who underwent 2nd look laparotomy, pathologic complete response rates (PCR) were 48.8% vs 48.1% (p ns). With a median follow-up of 81 and 31 months, median survival are 26 vs 29 months respectively, and 3-y survival rates (95% CI) are 42.8% (32 - 53%) vs 41.3% (25.9 - 56.7%).

Conclusion: We have obtained a better OCR rate with TAX-P compared to NOTAX-P regimens, but, contrary to the results of some randomized clinical trials, PCR rates, median survival and 3-y overall survival remain basically unchanged in our series.

964 POSTER DISCUSSION

Clinical development of Ovarex MAb-B43.13 monoclonal antibody for treatment of ovarian cancer: impact of immune responses and circulating CA125 levels on clinical efficacy

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OvaRex Mab-B43.13 is a murine monoclonal antibody (MAb) targeting the tumor-associated antigen CA125. Intravenous administration was associated with prolonged survival in patients (pts) with relapsed ovarian cancer, correlated with nonspecific (HAMA) and specific (Ab2) immune responses (Bolle, Proc. ASCO 19:476a, 2000). Paradoxically, prolonged survivals were seen in poor-risk pts, assessed by elevated circulating CA125 levels relative to pts with lower levels of CA125 (Noujaim A.A., Cancer Biother Radiopharm, in press). A prospective, randomized, placebo-controlled, double blind study of 345 pts with stage III-IV ovarian cancer was designed to determine clinical efficacy, safety, and biologic activity of OvaRex MAb administered after attainment of CR from primary chemotherapy. Preserving integrity of the blind, independent review was conducted from an initial cohort of 252 pts. Clinically meaningful immune responses were observed in >50% of the MAb-treated pts, measured by serum HAMA >5000 ng/mL and Ab2 >100 ng/mL associated with improved time to relapse (TTR). Pts with specific immune response (Ab2 serum level >100 ng/mL) demonstrated two-fold improved TTR to 18.9 mos vs. 7.4 mos in pts with Ab2 < 100 ng/mL. Irrespective of immune response, baseline CA125 prior to protocol treatment was a strong predictor of TTR, similar to previous reports (Makar, Gyn Oncol 49:73, 1993) and was confirmed to be a valid covariate for analysis of efficacy outcomes. In a poor prognosis subgroup (CA125 >20 U/mL), the proportion of pts surviving 6 months without disease relapse improved two-fold with OvaRex MAb therapy (relapse-free survival 79% vs. 39% in placebo-treated controls, p <0.05). Taken together, the favorable clinical outcomes in the high-risk pts with elevated CA125 levels support the proposed mechanism to induce immune responses to MAb + CA125 immune complexes, generated after intravenous MAb administration. Results from prospective, controlled trials confirm that OvaRex Mab-B43.13 frequently induces immune responses relevant to clinical efficacy, and provide rational approaches to development as an adjunct to treatment of ovarian cancer and possibly to treatment of other types of cancer associated with circulating serum CA125 levels.

965 POSTER DISCUSSION

Phase II clinical study of BBR 3464, a novel, bifunctional platinum analogue, in patients with advanced ovarian cancer

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BBR 3464 is a trinucleate platinum compound, differing from cisplatin in its structure, nature of the adducts formed, and pre-clinical spectrum of anti-tumour activity. The Phase I study of a 1 hour infusion every 28 days identified diarrhoea and myelosuppression as the dose limiting toxicities and initially 1.1mg/m2 as the recommended Phase II dose. Activity was observed in three patients, with respectively melanoma, pancreatic and lung cancer.

Purpose: The objectives of this Phase II study are to determine the efficacy of BBR 3464 in patients with ovarian cancer failing platinum-taxane regimens and to further characterise the toxicity and pharmacokinetic profile of this compound.

Methods: This is a multi-centre, open label, Gehan design study. Patients are stratified into two categories: those who relapsed following a response after 6 months from the discontinuation of chemotherapy and those who have not responded or have relapsed within 6 months.

Results: 28 relapsed and 18 refractory patients have been recruited to date and have received in total 164 infusions of BBR 3464. Five partial responses, confirmed by independent peer review, have been reported and in three of them a repeat scan for confirmation was obtained. In responding patients, the average interval between previous treatment and the first BBR 3464 treatment was 18 months. Toxicity data is available on 44 patients. The main toxicity seen so far is neutropenia (G3 n=7 (16%), G4 n=5 (11%)) which led to a dose reduction to 0.9mg/m2 in 6 patients. In addition, anaemia (G2 n=8, G3 n=1), thrombocytopenia (G2 n=1), nausea (G2 n=11, G3 n=8) and vomiting (G2 n=11, G3 n=5) were reported. Diarrhoea was observed (G2 n=14, G3 n=3) but was kept manageable by a policy of active intervention with loperamide. No clear signs of drug-related neurotoxicity were seen. One patient with pre-existing hypomagnesaemia and paraesthesiae experienced grade 2 paraesthesiae associated with course 3 of treatment. Since the haematological toxicities were reversible within 3 weeks and there was no evidence of cumulative renal or lung toxicity, a schedule of 0.9mg/m2 every 21 days, which in the ongoing Phase I trial was shown to be better tolerated and of a similar dose intensity, has now been introduced. Recruitment into the refractory category continues using this amended schedule. Efficacy and toxicity analysis is ongoing.

Conclusion: BBR 3464 is showing provisional evidence of activity in relapsed ovarian cancer.

966 POSTER DISCUSSION

Weekly paclitaxel and carboplatin followed by topotecan (TC-TP), as first-line therapy for patients with advanced epithelial ovarian cancer (AOC) suboptimally debulked. Updated preliminary results

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Objective: To evaluate clinical response (overall, complete and partial: cOR, cCR and cPR respectively), pathological CR rate (pCR), and toxicity, of the schedule TC-Tp, administered as first-line therapy in patients (pt) with AOC suboptimally debulked, defined as FIGO III-IV with residual disease (RD)> 1 cm.

Patients and Methods: Phase II design. TC-Tp consisted of 2 courses of TC (weekly Paclitaxel 60 mg/m2 + Carboplatin AUC 2, x 6 doses each course) separated by a 14-day rest period, and followed by 4 courses of Tp (Topotecan 1.5 mg/m2/d x 5d every 3 weeks). All pt received Tp after TC even if they had no response to TC. Prophylactic filgrastim was allowed after an episode of neutropenia grade 3-4, and Tp doses were reduced after other G3-4 toxicities. Second-look laparotomy was planned at least for pt with cCR after TC-Tp. In those pt with pCR or microscopic residual disease, consolidation with TCx1 + Tp x2 was recommended.

Results: Since March '99, 65 pt have been included and 50 pt have already completed TC-Tp. Preliminary results from the first 37 pt were presented in ASCO'01. Results from the first 50 pt are presented here. Mean age was 58 y (34-77). There were 78% stages III and 22% IV. Debulking surgery was performed in 86% of pt, but 88% had RD >2 cm.

Grade 3-4 toxicities with TC were anemia 2%, neutropenia 23%, thrombocytopenia 4%, alopecia 37% and nephrotoxicity 2%. Toxicity after Tp was anemia 13%, neutropenia 40%, thrombocytopenia 11% and alopecia 70%. Astenia was present in some pt but it was not properly registered. There were no toxic deaths. Other toxicities were G1-2 or absent.

Response rate after TC (and 95% CI) were: cOR: 82% (69 - 91%), cCR: 36% (23 - 50%) and cPR: 46%. After TCTp we found cOR: 78% (64 - 88%), cCR: 48% (34 - 63%) and 30% cPR.

The difference in cCR between TCTp and TC is 12% (95% CI: -0.85 to 16%). Five pt have achieved pCR until now (11.6%, 95% CI: 4 - 25%), but results of 2nd look are pending for another 5 pt with cCR. Fourteen pt received consolidation therapy and 19 pt other 2nd line therapies. With a