8045 POSTER

Feasibility of assessment and management of internal organ motion of cervix during radiotherapy by means of megavoltage computed tomography

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Background: Assessment of interfractional organ motion of cervix by megavoltage computed tomography (MVCT) during intensity-modulated radiotherapy (IMRT). Evaluation of impact of cervix soft tissue matching for management of cervix motion.
Methods and Materials: Ten patients with stage IIB-IVA cervical cancer underwent daily MVCT imaging. Interfractional organ motion was evaluated on 150 pre-treatment MVCT images by measuring shifts in their boundaries between the MVCT and planning kV CT scan in the anteroposterior (AP), laterolateral (LL) and superoinferior (SI) directions. Intrafractional patient movement was evaluated on 50 post-treatment MVCT images. Additional cervix soft tissue matching was performed for cervix alignment and impact of image-guidance on CTV-PTV margin was evaluated.
Results: Measured cervical motion (mean $\pm$ SD) was 0.4 ± 10.1 mm in anterior, -3.0 ± 6.9 mm in posterior direction, -3.5 ± 6.9 mm in left and 0.2 ± 4.5 mm in right lateral direction, 2.2 ± 8.0 mm in superior and 0.5 ± 5.0 mm in inferior direction. Compared to the cervix, larger uterine motion was observed. Patient movement during treatment was limited to 1.1 ± 1.25 mm, -0.26 ± 1.56 mm, and 0.22 ± 2.26 mm in AP, LL and SI direction respectively. Cervical alignment asked mean additional manual adaptation of 1.1 ± 9.5 mm in anterior, 0.8 ± 6.5 mm in posterior and 0.9 ± 5.9 mm in lateral direction. Cervix soft tissue matching can allow for a reduction of CTV-PTV margin of 10 mm in anteroposterior direction.
Conclusions: MVCT imaging can be used to study patient setup accuracy and internal cervical motion during IMRT. MVCT image guidance could be a valuable tool for management of cervical motion during IMRT.

8046 POSTER

Preliminary results of the ENDORAD trial: RAD001 (everolimus) monotherapy as second-line or third-line treatment of endometrial carcinoma: a phase II trial of GINECO group

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Background: The PTEN mutation was find in 40−60% of endometrial carcinoma, the loss of PTEN will activate the PI3K/AKT/mTOR pathway. RAD001 (everolimus) is an oral inhibitor of mTOR, an intracellular kinase that regulates cell proliferation and angiogenesis. Antitumor activity has been shown in a single-arm Phase-II trial in patients with recurrent endometrial carcinoma (Slomovitz and al, ASCO 2008).
Materials and Methods: A multicenter phase II study was conducted to assess efficacy and safety of mTOR inhibitor (RAD001) in patients (pts) with recurrent endometrial carcinoma refractory to chemotherapy. Inclusion criteria were disease not amenable to cure with surgery and/or radiation, a measurable progressive lesion(s) according to RECIST criteria, pretreatment with at least one line of chemotherapy with platinum salts, ECOG performance status <2, age $\geqslant$18 years. RAD001 was given at the dose of 10 mg/day until progression or intolerance. Primary endpoint was the rate of non progression at 3 months. A two step Simon design was used to include 44 patients. The first 22 included patients were evaluated for non progression at 3 months and for toxicity.
Results: Between 04/08 and 08/08, 22 patients were enrolled in 13 centers. Median age was 64 years (range 53−77). Histological subtypes were endometrioïd (64%), serous (23%) and other (13%). Histological grading was well, intermediate and poorly differentiated for 27%, 37%, and 18% respectively. Metastatic sites were pelvic 18%, peritoneal 27%, lymph nodes 59%, lung 55%, and bone 18%. Pts had received 1 (68%) or 2 (32%) lines of CT before inclusion. Median treatment duration was 72 days (range 4−119). Reported toxicity (G1−4) included fatigue (88%), diarrhea (50%), nausea vomiting (50%), dyspnea (43%), cutaneous rash (40%), anorexia (46%) and haematological (60%). G3−4 toxicities were dyspnea (4%), fatigue (36%), anorexia (13%), nausea (4%), diarrhea (4%), anaemia (11%), pneumonitis (4%), and infection (4%). There was no drug related death. 6 dose reductions have been reported, and treatment had to be temporarily interrupted in 23% of the patients due to toxicity (dyspnea 2, fatigue 1, and thrombopenia 2). There was one partial response and eight stabilized disease reported at 3 months (41%). Only 2/9 pts in the poorly differentiated group were not progressive at 3 months compared to 7/13 pts in other subgroups.
Conclusion: RAD001 shows a clinical benefit in pre-treated patients with recurrent endometrial carcinoma refractory to chemotherapy (first stage). According to the protocol, the study will continue to enroll 44 patients. Due to the results for pts with poorly or non-differentiated tumor, patients with this histological type will be excluded in the next step of the trial. Biological molecular analyses on tumor samples are on-going.

8047 POSTER

Feasibility of a modified outpatient regimen of intravenous/ intraperitoneal chemotherapy (IV/IP) in optimally debulked stage III ovarian cancer patients: A GEICO Study

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Background: The high rates of toxicities reported with I.P. chemotherapy appear to be a serious obstacle to widespread implementation of this approach in spite of the results of meta-analysis performed by National Cancer Institute that showed improved survival compared with IV therapy. The purpose of this study was to evaluate the toxicity of a modified outpatient IV/IP regimen in a routine clinical setting.
Methods: 51 women from Institutions of the Spanish Ovarian Cancer Group (GEICO) who were treated with the regimen: Day 1, IV Paclitaxel 175 mg/m^2, over 3h; Day 2, IP Cisplatin 100 mg/m^2 (option for 75 mg/m^2); and Day 8, IP Paclitaxel 60 mg/m^2 every 21 days, between February 2006 and November 2008, were included in this study. The planned treatment was six cycles of IP. CTCAE v 3.0 was used to grade toxicity.
Results: Median age 49 (range 36−75). The median time from surgery to first cycle of IP chemotherapy was 40 days (range 30 to 53). In 34 (67%) patients the IP catheter port was placed at initial surgery. Venous access devices were utilized in 50 (98%) patients. Five patients never initiated IP chemotherapy due to fluid leak from vagina (2), wound infection (1), catheter blockage (1) and patient refusal (1). Cisplatin was initiated at a dose of 75 mg/m^2 in 10 (21.7%) out of 46 women. Dose reduction occurred in 5.6% and 7.8% of the IP Cisplatin and IP Paclitaxel cycles respectively. Twenty-eight women (61%) completed all six IP cycles with 39 (85%) completing four or more IP cycles. Twenty-three patients were switched to IV chemotherapy. All patients received six courses of chemotherapy. Reasons for discontinuing IP therapy per patient were: catheter related 3 (6.5%), gastrointestinal 5 (11%), neuropathy 2 (4.4%), metabolic 1 (2.2%); abdominal pain 1 (2.2%), febrile neutropenia 1 (2.2%), patient refusal 3 (6.5%) and unknown 1 (2.2%). There were 14 cases (30.4%) of grade 3/4 neutropenia and 2 cases (4.3%) of febrile neutropenia. Grade 3/4 non-hematologic toxicities were nausea/vomiting (21.8%), renal/metabolic (11%), fatigue (10.9%), abdominal pain (4.3%) and neuropathy (4.3%). The median follow-up is 12 months [3.17−31.7]. Progression free survival at 12 months is 94% [95% CI: 86.0−100%].
Conclusions: The rate of completed planned treatment (61%) and the favourable toxicity profile reported support (IV/ IP) in routine practice. The optimal IP/IV regimen and duration of therapy have yet to be determined.

8048 POSTER

Weekly cisplatin or gemcitabine concomitant with radiation in management of locally advanced carcinoma cervix

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Introduction: Carcinoma cervix is the most common malignancy amongst females in India. With current evidence, concomitant chemoradiation with cisplatin is recommended for treatment of locally advanced carcinoma cervix. The use of non-platinum drugs in concurrent setting has not been well explored and hence two arm study was planned to compare the outcome of concomitant cisplatin or gemcitabine in locally advanced carcinoma cervix.
Material and Methods: Thirty six (36) patients of locally advanced cervical malignancy were evaluated in this study in term of response rate and complications. These patients were divided into two arms, sixteen (16) patients in cisplatin arm and twenty (20) patients in gemcitabine arm. Cisplatin and gemcitabine was given as i.v. infusion at dose of 40 mg/m^2

and 150 mg/m^2 respectively for 5 weeks concomitant with radiotherapy. All patients had received pelvic external beam radiotherapy to dose of 50 Gy/25fraction/5 weeks by four field box technique followed by intracavitary radiotherapy (3 sessions, each 7 Gy to point A).
Results: Median follow up noted was of 8.5 months (range 3−36 months) and 10.9 months (range 2−49 months) in cisplatin arm and gemcitabine arm respectively. At first follow up, 68.8% in cisplatin arm and 70% in gemcitabine arm had achieved complete response. Similar response rate was noted in different stages in both arms. None of the patients except one had developed grade 4 toxicity. Similar toxicity profiles were observed in both arms. In comparison to cisplatin arm, a higher number of patients in gemcitabine arm had developed grade 3 and 4 anemia (4/20 vs. 2/16), neutropenia (2/20 vs. 0/16) and thrombocytopenia (2/20 vs. 0/16). Grade 1/2 nausea was commoner in cisplatin arm as compared to gemcitabine arm (14/16 vs. 5/20). Local disease control, distant disease free survival and overall survival was 68.8% vs. 70%, 93.8% vs. 85%, 68.8% vs. 60% in cisplatin and gemcitabine arm respectively. None of patient in cisplatin arm had failed after achieving complete response. In gemcitabine arm, three patients had pelvic/ distant failure after achieving complete response.
Conclusion: Weekly gemcitabine had similar disease control and tolerable toxicity profile like cisplatin. Cisplatin arm was found to have edge over gemcitabine arm in longer follow up with sustained results. Gemcitabine may be used as alternative to cisplatin in patient with compromised renal function.

8049 POSTER

Cisplatin-based combination chemotherapy (CTX) consisting of docetaxel and cisplatin (DP) is still effective for patients with relapsed ovarian carcinoma (ROC) resistant or refractory to carboplatin-based CTX (TC: taxol/carboplatin)

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Purpose: To evaluate the efficacy and toxicity of DP for patients (pts) with relapsed EOC.
Methods: Eligible pts had histologically-confirmed serous, endometrioid, or transitional cell carcinoma of the ovary measuring more than 2 cm in diameter, age ⩽75 yrs, WHO PS ⩽ 3, adequate pulmonary, cardiac, hematopoietic, liver and renal functions, and written informed consent. The DP regimen was as follows: docetaxel, 60 mg/m^2 infused over 1 hr, days 1 and cisplatin 15 mg/m^2 infused over 2 hrs, days 1−5. The treatment was repeated at 4-week intervals.
Results: Forty eligible pts were enrolled in this study. The median age was 51 yrs (range, 41−64). All pts received more than 6 cycles of TC. Thirty-four of 40 pts (85%) had 1 or more previous chemotherapy other than TC. Histologic types were serous (33 pts), endometrioid (5 pts), and transitional (2 pts). After a median of 4 cycles (range, 2−10), we observed objective responses in 28 pts (70%), with 4 (10%) CRs and 24 (60%) PRs, and 12 (30%) NCs. Median overall survival time (MOS) for all 40 pts was 24.3 months (mo) (range, 4 to 78). MOS of pts achieving CR, PR, and NC were “not reached”, 23.6 mo, 8.2 mo, respectively (Log-rank, $p < 0.001$). The most frequent Grade 3−4 hematologic toxicities were; neutropenia 57.8%, anemia 43.3%, and thrombocytopenia 14.4%. Alopecia (Grade 1−2) occurred in 91.3%, but there was no grade 2 or 3 peripheral neuropathy, nephrotoxicity, or cardiotoxicity.
Conclusion: The DP regimen had a significant anti-tumor activity with acceptable toxicity and appreciable response duration for pts with relapsed OC resistant or refractory to TC. Several studies have demonstrated that cisplatin is more effective than carboplatin in almost all platinum-sensitive disease except OC (Lokich J: Cancer Invest 19; 756: 2001). In OC, carboplatin was reported to be equal to cisplatin in anti-tumor activity in “optimal” disease (GOG 158, AGO), but the equivalency was not demonstrated in “suboptimal” disease. We must reappraise cisplatin is an agent that should be included in the first line for platinum-sensitive OC.

8050 POSTER

Usefulness of FDG-PET/CT guided brachytherapy planning in patients with uterine cervical cancer

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Background: To evaluate the feasibility of FDG-PET/CT guided conformal brachytherapy treatment planning in patients with cervical cancer and compare dose-volume parameters with conventional treatment planning.
Materials and Methods: Seven patients with cervical cancer were included in this study. Brachytherapy simulation was done at external beam radiation therapy dose of 36 Gy. Patients underwent FDG-PET/CT scans with placement of the tandem and ovoid applicators. A target volume was determined and a treatment plan was generated that included dose–volume histograms and three dimensional (3-D) dose distribution displays. For each patient, comparison between conventional point A plan with PET/CT guided volume based plan was done. A PET/CT guided volume based plan was designed to cover clinical target volume (CTV), which included entire cervix shown on CT and residual tumor represented by FDG uptake on PET. The percent of volume receiving 100% prescribed dose (V100) and 90% prescribed dose (V90) were analyzed for CTV, bladder, and rectum.
Results: Five patients presented with FDG uptake on tumor and 2 patients had no discernable uptake. The median V100 and V90 of CTV in point A plan were 73.7 and 79.9%, respectively. CTV coverage was significantly improved in PET/CT guided plan with 88.0 and 92.5% of median V100 and V90 ($p = 0.06$, $p = 0.06$), respectively. V100 and V90 of both bladder and rectum were not significantly different.
Conclusions: The visual target localization was facilitated by using CT with PET fusion. PET/CT guided brachytherapy plan was superior to conventional point A plan in terms of the target coverage without increasing the dose to the bladder and rectum, making optimized 3-D brachytherapy treatment planning possible.

8051 POSTER

Final results of a phase I study of pegylated liposomal doxorubicin + gemcitabine in prolonged infusion in patients with recurrent ovarian cancer less than one year

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Background: We present the final results of a phase I study with the combination of Pegylated liposomal doxorubicin (PLD) (standard treatment) and Gemcitabine (G) in a prolonged infusion (PI) (10 mg/m^2/min) in order to know if we can enhance the therapeutic index of this association in patients with platinum-resistant ovarian cancer.
Materials and Methods: Eligible criteria included: recurrent epithelial ovarian cancer (REOC) with a platinum-taxane free interval <1 year, primary or secondary treatment with platinum and taxane, age <80 years, Karnosky ⩾ 60% and normal organ function.
The starting dose of G was 1500 mg/m(2) PI q 2 weeks (± 250 mg/m^2 in PI G titration depending on toxicity) followed by PLD 35 mg/m^2 q 4 weeks. Pharmacokinetic and pharmacogenomic analyses were performed on days 1 and 15 of the first cycle. The primary end point was to determine the dose-limiting toxicity (DLT), the maximum tolerated dose (MTD) and the recommended dose. The toxicity was studied only in patients who received almost two cycles.
Results: From December 2005 to July 2008, 36 patients (pts) were registered. 1 pts was not eligible and 6 were non-evaluable for toxicity due to early progression. In the first step, 2 out of 4 pts had DLT consisting on grade 4 neutropenia and grade 3 stomatitis. 5 pts entered in the next step, G1250/PLD35, with different tolerance between “frail pts” (heavily-pretreated pts (> 6 cycles) and/or >70 years) and “non frail pts” so we divided pts up into two groups. Frail pts were treated with G1000/PLD35 and 3 of 12 pts experienced DLT while non frail pts were treated with G1250/PLD35 and 4 of 10 developed DLT. Dose reduction was necessary due to late toxicity (stomatitis (85%) and dermatitis (61%)). The most common grade 3/4 adverse effects were neutropenia (43%), stomatitis (35%), dermatitis (21%) and hand-foot syndrome (14%). PLD did not affect the pharmacokinetic of G or its metabolites. Response rate: 17% complete responses (6/35), 26% partial responses (9/35) and 20% stable disease (7/35). The median time to progression and median overall survival were 230 days (95% CI, 65−394) and 417 days (95% CI: 281−552), respectively.
Conclusions: Preliminary results suggest that Gemcitabine 1000 mg/m^2 in a prolonged infusion q 2 weeks + Pegylated liposomal doxorubicin 35 mg/m^2 q 4 weeks is an active combination with tolerable toxicity so these are the recommended doses for a phase II study in REOC.

8052 POSTER

Weekly paclitaxel in the treatment of relapsed ovarian and primary peritoneal cancer - Royal Marsden Hospital experience

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Background: Single agent weekly paclitaxel has been reported to have significant activity in patients with ovarian and primary peritoneal cancer,