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Is micro-multileaf collimator really necessary to treat small intracranial tumors?

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Objective: To assess the real need of micro-multileaf collimator for fractionated radiotherapy in the treatment of small intracranial tumors.

Methods: BrainLAB micro-multileaf (3 mm/leaf) collimator and standard Siemens multileaf (10 mm/leaf) collimator were compared using 6-MV photos from Siemens Primus linear accelerator and the BrainSCAN 4.03 planning software. A cranial phantom was created by molding wax into a patient fixation mask. Two glass spheres of 15-mm and one of 22.5-mm diameter were inserted side-by-side in the center of the phantom (anatomical position of hypophysis). In order to use the same software (BrainSCAN 4.03) for the comparison, the Siemens multileaf (10 mm) collimator was simulated using three 3-mm BrainLAB micro-multileafs (9 mm instead of 10 mm) together. Using three different GTVs (two spherical volumes of 15- and 22.5-mm diameter, and one complex GTV composed by two 15-mm spheres side-by-side), we compared the dosimetry obtained by either one field or five non-coplanar fields using the 3-mm micro-multileaf collimator or the same geometry using the 9-mm standard multileaf collimator by turning the collimator by steps of 20 degrees (up to a total of 5 rotations [0, 20, 40, 60, 80 degrees] in single-beam situation or 3 rotations [0, 20, 40 degrees] using five non-coplanar beams) in order to smoothen the dose distribution.

Results: Our data demonstrate that, turning the collimator either every day or during the same fraction results with a dose distribution as good as the one obtained by the micro-multileaf collimator. Dose-volume histogram analyses reveal that the volume obtained by subtracting the volume covered by the 95% isodose from the exact volume of the GTV (V95% - VGTV) is almost identical either in one-sphere situation (0.000 ml vs. 0.008 ml; respectively), or in the two-sphere complex volume situation (0.050 ml vs. 0.056 ml; respectively) when comparing the 3-mm micro-multileaf collimator with the 9-mm standard multileaf collimator with collimator rotation.

Conclusion: We conclude that, in the treatment of GTVs 20 mm diameter or more, the physical dose distribution obtained either in the GTV or in the surrounding normal tissues is similar in both techniques. Using a good fixation system and turning the standard multileaf collimator by one or two steps of 20 degrees when using multiple non-coplanar fields, there is no need for 3-mm micro-multileaf collimator in order to treat either spherical or complex GTVs.

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Quantification of late complications after radiation therapy

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Purpose: An increasing number of patients survive cancer after having received radiation therapy. Therefore, the occurrence of late normal tissue complications among long term survivors is of particular concern.

Methods: Sixty-three patients treated by radical surgery and irradiation for rectal carcinoma were subjected to an unconventional sandwich therapy. Preoperative irradiation was given in four fractions of 5 Gy each applied within 2 or 3 days; postoperative irradiation consisted mostly of 15 x 2 Gy (range 20 to 40 Gy). A considerable proportion of these patients developed severe late complications (Svoboda et al., Radiother. Oncol. 1999; 53: 177-187). The data allowed a detailed analysis of complication kinetics leading to a new model which was tested using data from the literature.

Results: Data on late complications (grade * 3) were obtained for eight different organs with a follow-up of up to ten years. For the various organs, the percentage of patients being free from late complications, plotted as a function of time after start of radiation therapy, was adequately described by exponential regression. From the fit, the parameter pa was obtained, which is the percentage of patients at risk in a given year developing a complication in a given organ during that year. The rate pa remained about constant with time. Following sandwich therapy, the annual incidence of complications in bladder, ileum, lymphatic and soft tissue, and ureters was about the same (pa = 10 to 14% per year), whereas complications in bone or dermis occurred at lower rates (4.7 or 7.5% per year, respectively). From numerous data sets collected from published reports, three types of kinetics for the occurrence of late effects after radiotherapy were identified. Type 1: purely exponential kinetics; Type 2: exponential kinetics, the slope of which decreased exponentially with time; Type 3: curves composed of two components; a fast initial decline followed by an exponential decrease.

Conclusion: The results indicate that the hazard of developing late complications after irradiation remains about constant for many years. Thus, it might become necessary to change frequency and duration of follow-up after radiation therapy and to extend patient's information on long-term radiation risks.

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A prospective randomized, double-blind multicenter-trial on radiation therapy for neovascular age-related macular degeneration (armd)

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Purpose: The efficacy of external radiation therapy on choroidal neovascularisation (CNV) due to ARMD should be proved in a randomized, double-blind multicenter trial.

Methods: 205 pat were randomized either to treatment with 8 fractions of 2 Gy (n=101) or to a placebo-group with 8 fractions of 0 Gy external beam therapy (n=104). Pat. and physicians were blinded with regard to applied treatment. Only pat. with classic or occult CNV, visual acuity > 20/320 on the ETDRS-chart, lesion size < 6 disc areas, history of visual symptoms < 6 month and absence of foveal hemorrage were treated. Outcome measure was the difference in visual acuity between baseline and after 1 year follow up.

Results: 183 pat. were evaluable after 1-year follow up. The mean reduction in visual acuity was 3.5 + 4.7 lines in 88 pat. of the treatment group and 3.7 + 3.8 lines in 95 pat. of the placebo-group. This difference was statistically not significant (p=0.53; Mann-Whitney-U-Test). At 1 year 51.1% of treated pat. and 52.6% of the placebo-group lost 3 or more lines on the ETDRS-chart (p=0.88). Visual acuity in pat. with classic CNV dropped by 3.7 + 4.4 in 33 pat. of the treatment group vs. 4.3 + 3.9 lines in 36 pat. of the placebo-group (p=0.47). In pat. with occult CNV visual capacity dropped by 3.4 + 4.9 (n=55) in the treated - vs. 3.4 + 3.8 lines (n=59; p=0.8)) in the placebo-group.In the irradiated group no side-effects were seen.

Conclusion: The dose of 8x2Gy applied in 8 fractions provided no benefit as a treatment of classic or occult CNV due to ARMD after 1 year.

Gynaecological cancer

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International variations in the surgical management of advanced ovarian cancer between countries participating in scotroc: a large prospective international phase-3 trial

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Aim: International comparisons of ovarian cancer survival data have led many to conclude that the quality of treatment, particularly surgery, in the UK is significantly inferior to other parts of the world. However, these data come from cancer registries, are retrospective, and cannot be considered definitive. We have therefore conducted an indepth analysis of initial surgery carried out on patients in a large scale prospective international clinical trial [SCOTROC] in which information on all other biological and treatment variables should allow valid conclusions to be drawn regarding the impact or outcome of variations in surgical practice.

Methods: Surgical records were inspected in detail on 899 patients representing 83% of the 1077 patients entered into the SCOTROC trial [international prospective phase-III trial comparing carboplatin/taxol vs carboplatin/taxotere in advanced ovarian cancer]. 689 of these were from the UK and 388 from centres elsewhere in Europe, and in Australasia and USA.

Results: Systematic surgical differences were found between patients recruited by UK and non-UK centres. In FIGO stage 1C, non-UK centres were more likely to undertake aggressive staging procedures. Para-aortic lymphadenectomy was performed in 52% of stage 1C patients outwith the

UK vs 5% in UK centres [Fisher's: p<0.0001]. In FIGO stage 3 aggressive debulking procedures were more likely to be performed in non-UK centres. 'TAH/BSO & Omentectomy'was performed in 62% of cases from non-UK centres vs 49% in UK centres [p=0.0002]. These differences corresponded to a greater likelihood of optimal debulking of tumour [non-UK centres 71% vs 58%: p<0.0001]. This increased surgical activity was associated with a longer operating time. [Non-UK centres, median=136 minutes; UK centres, median=95 minutes: Mann Whitney: p<0.0001].

Conclusion: This study demonstrates clear differences in surgical practice among gynaecologists referring patients for entry into this clinical trial, comparing the UK with non-UK centres. These differences in surgical practice are particularly relevant to the management of stage 3 tumours where there appears to be a greater likelihood of residual disease >2cm following UK procedures. As this is known to be a key prognostic factor, these are potentially large enough to impact significantly on treatment outcome, and might explain some of the variability in survival outcome seen in the EUROCARE studies. Survival data are awaited.

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Conservative treatment of ovarian borderline tumor

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Purpose: The aim of this study is to assess the clinical outcome and fertility of patients treated conservatively for a low malignant potential ovarian tumor (LMPOT).

Methods: Forty-four followed-up patients treated with conservative management for a stage I (n = 32) or II and III (n = 12) LMPOT were followed-up. 33 patients underwent a unilateral adnexectomy and 11 had a cystectomy (bilateral in 1 patient; with contralateral adnexectomy in 5 patients).

Results: The recurrence rates following radical surgery, adnexectomy and cystectomy were respectively: 5.7%, 15.1% and 36.3% (p < 0.01). None of the recurrences in the patients who were initially treated conservatively were under the form of ovarian carcinoma. Five patients who had recurrence underwent again a conservative management of these recurrences. All patients treated conservatively are alive and disease-free. Seventeen pregnancies (15 spontaneous) were obtained in 14 patients. Thirteen pregnancies were obtained in patients with stage I disease and 4 in patients with stage III.

Conclusion: The conservative management of LMPOT increases significantly the risk of recurrence but without affecting the overall survival. Such a management offered a chance of having spontaneous pregnancies even in patients with advanced stage of the disease (noninvasive peritoneal implants). Conservative management could be proposed in young patients wishing to preserve their fertility. But careful follow-up will be required to detect any recurrence in the ovaries.

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Epirubicin/paclitaxel/carboplatin (TEC) vs paclitaxel/carboplatin in first line treatment of ovarian carcinoma figo stage II b-IV. Preliminary results. A GINECO randomized trial

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Purpose: The objective of this randomized trial was to demonstrate whether the three drug chemotherapy regimen (TEC) increases overall survival over two drug (TC).

Methods: Between 11/1997 and 02/2000, 1281 patients were randomized to receive 6 cycles of paclitaxel (175 mg/m2, 3 h iv) followed by carboplatin (AUC 5, Calvert formula) with (TEC) or without (TC) epirubicin (60 mg/m2 iv prior to Paclitaxel) on a 3 weekly schedule. Patients (pts) were stratified for stage and residual tumor (rT) (II-III + residual T ≤ 1 cm = Strate 1/IV and II-III + residual rT > 1 cm = Strate 2).

Results: Patient characteristics are well balanced between two arms (1190 pts). NCI-CTC toxicity of 3-4 grade was observed in 54% of the cycles of TEC and 30% of TC. Hematologic toxicity was grade 3-4 in 68% of the patients in TEC arm, versus 30% TC arm. Non hematologic toxicity was not significantly different between TEC and TC except for nausea and vomiting. Adjonction of epirubicin did not increase cardiac toxicity. There is no significant difference in progression free survival between TEC and TC (1190 pts). But there is a trend in favour of TEC in strate 1, 323 events/605 pts, med 18 (16/21) vs TC 333/585, med 17 (15-19). There is no difference between TEC and TC for overall survival. Follow up and analysis will be updated in autumn 2001.

Conclusion: this is the first trial evaluation of standard chemotherapy versus three drug regimen. Both regimens are feasible. TEC induces more hematologic and vomiting toxicities than TEC. Until today there is no advantage in terms of overall survival of TEC over TC.

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ACTION + ICON1: two parallel randomised phase III trials comparing adjuvant chemotherapy to no adjuvant chemotherapy following surgery in women with high risk early ovarian cancer

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Background: Despite a number of small randomised trials it is not clear whether adjuvant chemotherapy improves survival in women with early stage epithelial ovarian cancer.

Method: We carried out two parallel international, multicentre, randomised trials ICON1 (International Collaborative Ovarian Neoplasm studies) and ACTION (EORTC: Adjuvant Clinical Trial In Ovarian Neoplasm) to compare adjuvant platinum-based chemotherapy against chemotherapy delayed until indicated, in women with surgically resected early ovarian cancer. The primary outcome was length of survival.

Findings: 925 (477 in ICON1, 448 in ACTION) patients were randomised from 124 centres in 13 countries; 465 to adjuvant chemotherapy and 460 to no adjuvant chemotherapy. The median age was 55 years with over 90% patients being FIGO stage 1. The major histological cell types were serous (34%), mucinous (20%), endometrioid (25%) and clear cell (14%). Differentiation of disease was classified as poor in 31% of patients, intermediate in 46%, and well in 22% of patients. The patient characteristics were similar in both treatment groups. With over 3 years median follow-up for survivors, the hazard ratio for recurrence-free survival is 0.64 (95% confidence interval 0.50 to 0.83), p = 0.001, in favour of adjuvant chemotherapy. For overall survival the hazard ratio is 0.68 (95% confidence interval 0.51 to 0.92), p = 0.01, in favour of adjuvant chemotherapy. These results translate into an absolute difference of 7% in overall survival at 5-year from 75% in the no adjuvant chemotherapy to 82% in the adjuvant chemotherapy.

Preliminary Conclusion: Adjuvant chemotherapy improves both recurrence-free survival and overall survival. The clinical interpretation of these results will be discussed.

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CA125 response and disease stabilisation are associated with estrogen receptor expression in a phase II trial of letrozole in ovarian cancer

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Purpose: We are exploring the therapeutic potential for estrogen receptor (ER) targeted approaches in ovarian cancer. In a phase II trial of the aromatase inhibitor letrozole (Femara) in relapsed ovarian cancer, we have investigated the relationship between antitumor response to letrozole and several markers relating to estrogen regulation predicted by our experimental ovarian cancer models.

Methods: 60 patients were treated with letrozole (2.5 mg daily) at CA125 relapse. To date, 45 patients are evaluable for response by CT scan and 48 by CA125 criteria. ER and progesterone receptor (PR) expression were measured in primary tumors by immunohistochemistry (IHC) using a scoring system ranging from 0 to 300 (product of % cells positive and intensity). EGF receptor and erbB2 were also measured by IHC.

Results: After 3 months treatment, using UICC criteria, letrozole produced no complete or partial responses, 8 patients had stable disease and 37 progressed. Using CA125 criteria, 5 patients had a partial response (> 50% fall), 13 had a stable value at 3 months (<50% rise) and 30 had a clearly progressing value. The UICC stable disease group had a significantly higher ER (p=0.032) and PR value (p=0.0096) than the progressive disease group and a combination of these ER > 150, PR > 70 was associated very strongly with stable disease (p < 0.0001). Using CA125 criteria, comparison of the CA125 stable/responding disease with progressive disease again indicated