20 ORAL

The effect of treatment interruptions in the postoperative irradiation of breast cancer

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Purpose:; To determine the outcome of the treatment interruptions in the postoperative irradiation of breast cancer, 853 patients treated in the years 1990-1999 inclusive were retrospectively analysed.

Materials and methods: Median age was 49 years(21-87). The median follow-up was 69 months(7-166). The most common histpathologic diagnosis was invasive ductal carcinoma (80%). Tumour distrubition by pathologic T stage was:T1; 38%, T2; 51%, T3; 7%, T4; 2%, TX;2%. Locally advanced breast cancers who received neoadjuvant chemotherapy were not included. Fivehunderedandfortysix (64%) patients were treated with mastectomy and 307(36%) patients were treated with breast conserving surgery; 20(2%) patients did not have axillary dissection. There were no axillary lymph node involvement in 268(31%) patients, 1-3 lymph nodes were positive in 300(36%), 4 and more lymph nodes were positive in 265(31%) patients. All of the patients had treatment with a Co60 unit or 4 MV x-rays. All patients with breast conserving surgery had breast irradiation. Chest wall irradiation were given to the patients who had axillary involvement.T3 and T4 tumours had chest wall irradiation regardless of axillary status. Lymphatic fields were selected due to the number of involved nodes. The dosage and treatment details will be presented. Patients are grouped due to the duration of treatment interruption. Grouping will be given in detail. Only the groups who had statistically significant results are mentioned in the abstract. Group A had 348(41%) patients who had no treatment break or interruptions of 7 days or less. Group B had 505(59%) patients who had treatment interruptions of 8 days or more. Locoregional control(LC), overall survival(OS), and disease free survival(DFS) rates were estimated by Kaplan-Meier method. Multivariate analyses were done by Cox model testing the parameters age, menauposal status, T stage, grade, histopathologic subgroups, axillary status, type of surgery, systemic treatment and duration of radiotherapy interruption.

Results: For all patients LC, OS and DFS for 5 years were 95%, 78%, 65% respectively and 10 years rates were as follows; 87%, 62%,54%. LC control rates for group A for 5 and 10 years were 94% and 90% respectively and it were 89% and 86% for group B. The difference was statistically significant (p=0,0196). OSS rates for group A for 5 and 10 years were 82% and 64% respectively, and it were 74% and 60% for group B (p=0,0267). DFS rates for group A for 5 and 10 years were 67% and 58% respectively and it were 63% and 52% for group B(p=0,05). In multivariate analyses treatment interruptions of 8 days or more and premenauposal status had appeared to be independent adverse prognostic factors on LC(p=0,036 and p=0,004, respectively).

Conclution: This retrospective study shows that treatment interruptions of 8 days or more during postoperative irradiation of breast cancer had adverse effects on outcome of treatment

21 ORAL

Histologic type of local recurrence and prognostic significance in breast conservation vs. mastectomy in invasive breast cancer: A 20-year update of a randomized trial

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Aim: The main objectives are to analyse the histologic pattern of local recurrence in breast conserving therapy (BCT) vs. mastectomy (M) and to address the prognostic significance related to histologic type of local failure.

Material and methods: During 1983-1989 the Danish Breast Cancer Cooperative Group, DBCG, conducted a randomized trial, DBCG 82-TM, comparing BCT with M. A total of 1142 patients with invasive breast cancer were accrued and allocated to either type of surgery. The patients were followed until 2002 allowing up to 20 years of observation. Data set covering conventional patient- and tumour characteristics as well as type of surgery and adjuvant regimens were registered. Clinical records and histologic slides underwent revision. In case of a local failure within the ipsilateral breast (BCT) or chest wall (M) a discrimination was made between a true local recurrence vs. a new primary tumour. Further, a distinction was carried out between local relapse as a first event or a second event following regional and / or distant disease.

Results: Regarding local recurrence as a first event, the analysis revealed that true recurrence predominated as local failures in M versus new primaries in BCT. Outcome measures indicate that true recurrence as a first event bears a worse prognosis compared with new primaries. Crude local recurrence rate amounted to 10% by at least 1o years of observation in either type of surgery. In BCT new primaries constituted 57% of local failures, while the figure in M reached 10%. Overall survival was 58% and did not differ significantly between BCT vs. M by 20 years of observation. Further details of the analysis will be presented.

Conclusion: It is concluded that the histologic local recurrence pattern regarding a first event differs between BCT and M and that outcome measures indicate a worse prognosis in true recurrence vs. new primaries. Overall survival in the trial did not differ significantly between BCT vs. M by 20 years of observation.

22 ORAL

Total tumour tissue levels of tissue inhibitor of metalloproteinases-1 as a prognostic marker in breast cancer: an EORTC validation study of 2984 patients.

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Background: Today, prognostic stratification of breast cancer patients with the aim of planning appropriate treatment for every patient is based on classical prognostic parameters: Lymph node status, tumour size, grade of malignancy, age, and hormone receptor status. Still, prognostic stratification is not complete, which results in over-treatment of a large number of patients.

We have previously demonstrated that total tumour tissue levels of tissue inhibitor of metalloproteinases-1 (TIMP-1) are associated with prognosis in patients with primary breast cancer. Furthermore, we have shown that TIMP-1 may be useful as a prognostic marker in combination with plasminogen activator inhibitor type-1 (PAI-1). The present study aims at validating these findings and has been conducted as an EORTC collaboration.

Materials and Methods: The study includes 2984 patients with primary breast cancer, 51% of whom were lymph node-negative and 49% lymph node-positive. The median age of the patients was 57 years. By use of an established TIMP-1 enzyme-linked immunosorbent assay (ELISA), total levels of TIMP-1 were measured in cytosol extracts of tumour tissue from the patients. Prior to measuring TIMP-1 in the extracts, the ELISA was thoroughly validated. Levels of urokinase-type plasminogen activator (uPA) and PAI-1 have previously been determined in these tumour tissue extracts.

Results: Levels of total TIMP-1 in the tumours showed a log-normal distribution (median 14.0 ng/mg protein, range 0-336 ng/mg). Univariate survival analysis showed a significant relationship between higher levels of tumour tissue TIMP-1 (continuous log-transformed variable) and poor prognosis with regard to recurrence-free as well as to overall survival ($p<0.001$). By use of isotonic regression analysis, we chose a cut-point to classify tumours as TIMP-1-low or TIMP-1-high. High levels of TIMP-1, then, were significantly associated with both recurrence-free and overall survival. In a multivariate model including uPA and PAI-1, TIMP-1 was significantly associated with shorter recurrence-free survival both when included as a continuous log-transformed variable ($p=0.003$) and when included as a dichotomised variable using the above-mentioned cut-point ($p=0.002$).

Conclusions: This study validates the findings of our first study demonstrating an association between total tumour tissue levels of TIMP-1 and prognosis in patients with primary breast cancer. Furthermore, it confirms that TIMP-1 may be useful as a prognostic marker in combination with PAI-1. By conducting the present study, we have added substantial positive information on the use of TIMP-1 as a prognostic marker in breast cancer and have made the first attempt to an identification of a cut-point for dividing tumours into TIMP-1-high and TIMP-1-low ones.

23 ORAL

Factors influencing the number of sentinel lymph nodes removed in breast cancer

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Background: The purpose of this analysis was to determine factors associated with the removal of multiple sentinel lymph nodes (SLNs) and whether removal of multiple SLNs results in a lower false-negative rate.

Methods: In the ALMANAC audit phase, 31 surgeons in 17 centres throughout the UK operated on 842 breast cancer patients. The SLN was

identified using the combined technique (Nanocoll® +blue dye) followed by standard axillary dissection.

Results:

Variable	Number of SLN removed		p-value
	single	multiple	
False-negative rate	9.2%(9/98)	4.9%(9/182)	<0.05
Age <50years	33.3%(55/165)	66.7%(110/165)	0.002
>50years	38.7%(242/625)	61.3%(383/625)	
BMI <30	30.4%(125/411)	69.6%(286/411)	<0.001
>30	45.9%(45/98)	54.1%(53/98)	
Tumour location			
Outer quadrant	30.9%(101/327)	69.1%(226/327)	0.014
Inner quadrant	42.6%(55/129)	57.4%(74/129)	
Centre*	25%(3/12)	75%(9/12)	
Tumour size <2cm	33.2%(140/422)	66.8%(282/422)	0.577
2-5cm	37.4%(73/195)	62.6%(122/195)	
>5cm*	50%(4/8)	50%(4/8)	
Tumour histology			
Invasive Ductal Carcinoma	34.2%(158/462)	65.8%(304/462)	0.888
Invasive Lobular Carcinoma	38.6%(27/70)	61.4%(43/70)	
Mixed	33.3%(17/51)	66.7%(34/51)	
Special types	35.6%(16/45)	64.4%(29/45)	
Tumour grade 1	35.4%(45/127)	64.6%(82/127)	0.335
2	33.9%(95/280)	66.1%(185/280)	
3	35.6%(72/202)	64.4%(130/202)	
Drainage seen on lymphoscintigram			
Yes	32.8%(190/579)	67.2%(389/579)	<0.001
No	49.5%(100/202)	50.5%(102/202)	
Time interval between radioisotope injection and axillary incision			
3-12hrs	29.4%(65/221)	70.6%(156/221)	0.017
12-24hrs	39.4%(124/315)	60.6%(191/315)	
24-36hrs	28.9%(24/83)	71.1%(59/83)	
Axillary nodal metastases	30.5%(89/292)	35.2%(173/491)	0.096

*Not included in the analysis as number of cases is too small for meaningful comparison

Conclusion: The ability to identify multiple SLN, when they exist, lowers the false-negative rate of SLN biopsy. Factors associated with identification of multiple SLNs are: younger age; low BMI; tumours in the outer quadrant; SLN visualization of lymphoscintigram and <12 hours time interval between the radioisotope injection and axillary incision. Tumour size, grade, histology and axillary nodal metastases showed no significant association.

Radiotherapy and radiobiology

24 ORAL

Cost and economic evaluation of radiotherapy. Activity-based costing and modeling techniques

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The rapidly expanding technological evolution and demand for health care services, together with budgetary restrictions, have resulted in an increasing interest in the economic aspects of medical interventions and in the need for accurate cost data of the treatments we deliver.

Accurate cost data of radiotherapy activities and products are however scarce. Activity-Based Costing (ABC) is a refined cost-accounting technique that calculates product costs by allocating resource costs based on activity consumption. Its potential in the field of radiotherapy was demonstrated by developing an ABC model for the Leuven radiotherapy department.

Despite the high cost of equipment, wage costs are the most important component, consuming up to 60% of the total costs. Hence, daily radiotherapy delivery, a highly labour-intensive activity consuming the largest proportion of machine (and thus personnel) time, is the most costly of all radiotherapy activities. As a consequence of this, the number of fractions and the treatment time per fraction are the most important parameters affecting the ultimate product cost. These findings should be recognised when evaluating new developments in radiotherapy, such as hyperfractionation, conformal and intensity modulated radiotherapy, which, besides requiring more complex treatment preparation, also require more treatment time, and thus translate into higher costs.

Whether these higher costs are justified should be evaluated in economic analyses, in which the relation between costs and outcome is made explicit. Since it is frequently impossible to obtain all necessary cost and outcome data from randomised trials, decision analytic models, such as Markov models, are often used instead.

Based on this methodology, two radiotherapy treatment strategies have been analysed. The models were built on literature data on effectiveness and on cost data (predominantly) obtained through the ABC program. The immediate and delayed costs (from a societal viewpoint) and effects were compared.

CHART in non-small cell lung cancer (NSCLC) was found to be cost-effective compared to other NSCLC therapies reported in literature. The ex ante cost-effectiveness analysis of the internal mammary and medial supraclavicular (IM-MS) lymph node chain irradiation, currently under investigation in an EORTC study, showed IM-MS irradiation to be less costly, as well as more effective, from a long-term societal perspective. These results suggest that nor CHART, nor IM-MS irradiation, should be denied to patients on clinical or economic grounds.

It is however well known that multiple barriers can act against the implementation of scientific evidence into daily clinical practice. Whether financial aspects may play a role was analysed for the irradiation of bone metastases.

Although literature evidence converges towards the use of single fractions for the irradiation of uncomplicated metastatic bone pain, practice surveys have demonstrated that this schedule remains infrequently used. Our calculations, comparing the actual cost of different palliative radiotherapy schedules with the reimbursement these treatments generate in Belgium, now and in the past, show that the incentives imbedded in the reimbursement system may indeed affect the treatment choice.

25 ORAL

Repopulation in human squamous cell carcinoma FaDu: possible impact of the impairment of recovery from sublethal damage repair

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The so called time factor of fractionated radiotherapy has consistently been observed in clinical and experimental squamous cell carcinomas (SCC). The time factor might be explained by several mechanisms, including increasing cellular radioresistance, increasing hypoxia, selection of highly radioresistant and/or rapidly proliferating subclones, and rapid repopulation of clonogenic cells. It is generally agreed that accelerated repopulation of clonogenic tumor cells is the major cause of this phenomenon, but the underlying mechanisms are not well understood. We undertook a series of experiments on the human FaDu-SCC in nude mice to gain a better understanding of the kinetics and the mechanisms underlying the time factor and repopulation during fractionated irradiation. Functional endpoint of these studies was permanent local tumour control. Human FaDu-SCC were transplanted s.c. to the right hindleg of NMRI (nu/nu) mice from our specific pathogen free breeding facility. Local irradiations were given under ambient or under clamp hypoxic conditions using 200 kV x-rays. A variety of irradiation schedules including different number of fractions (3 to 18) in different overall treatment times (3 to 36) were applied. The schedules were determined by application of a top-up dose. After end of irradiation animals were observed for at least 120 days to detect virtually all regrowing tumours. Maximum likelihood analysis was used for comparison of experimental arms and for modelling. Typical experiments included at least 6-8 dose groups per experimental arm and at least 6-8 tumours per dose group. The functional data were complemented by immunohistochemical studies.

For FaDu a temporal coincidence between acceleration of repopulation and reoxygenation was found. The onset of reoxygenation in FaDu-SCC suggests that the latter might be the stimulus for repopulation. Increased necrotic cell loss by preirradiation of the tumour bed resulted in longer clonogen doubling times, implying that a decreased necrotic cell loss in response to irradiation might be the link between reoxygenation and repopulation. Increasing BrdU labelling indices, as well as a decreasing capacity for recovery from sublethal damage during the course of irradiation, suggests that a higher cell production rate may also contribute to repopulation. Staining intensity for the EGF-receptor decreased after start of irradiation to increase again after 24 days, i.e. in parallel to the acceleration of repopulation, suggesting that EGF signal transduction pathway might be involved in this phenomenon. Overall, the results indicate that the kinetics of repopulation of FaDu-SCC in response to fractionated irradiation is determined not only by intracellular processes but also by a complex interaction of proliferation parameters with a changing microenvironment.