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.

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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.