TUESDAY 23 SEPTEMBER 2003

Teaching Lectures

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Breast cancer radiotherapy - new techniques

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Background: Postoperative radiotherapy (RT) for breast cancer has been shown to reduce the LR rate with a factor of 3-4. Although this reduced LR rate results in an increase in breast cancer specific survival, no increase in overall survival was observed in the early days, due to an increase of cardiovascular deaths. However, trials started after 1975 do show a 10% improved overall survival, without an increase in cardiovascular deaths. Despite this optimism, caution should be expressed regarding unknown consequences of combinations of regional RT with newer cardiotoxic chemotherapy agents. Consequently, the main aim of new radiation techniques is to reduce dose to normal tissues as heart and lung. In addition, the new techniques aim for a more homogeneous dose distribution, to improve the cosmetic results.

Techniques: Whole breast RT is usually given with 2 tangential (wedged) fields. This technique is simple, but parts of heart and lung are often included in the high dose region, and it may yield a fairly inhomogeneous dose distribution. Improvement of this technique may be obtained by "geometric optimization", i.e. with these techniques it is tried to move the heart away from the breast, like RT in prone position, or RT during deep inspiration breath hold. Since these positional changes may not be applicable for all patients, other more general applicable approaches are being sought, consisting of "technical improvements". Several IMRT techniques have been described, yielding a more homogeneous dose distribution in the breast, and less dose to the heart. Techniques are being developed optimizing both the beam orientation and beam intensity. Optimal 2-beam orientations have been shown to correspond to a hinge angle of approximately 186° and 180° ±20°, respectively. A problem in the optimization routines for IMRT, however, is that there is no golden standard to delineate the CTV (breast tissue). In addition, the relations between the 3D dose-distribution and the LR rate and cardiac death are not known. Consequently, IMRT techniques are often optimized using rather arbitrarily chosen cost functions.

Another challenging area to reduce cardiac dose, is RT of the internal mammary chain (IMC). Although the value of IMC irradiation is subject of a large EORTC trial, IMC RT is clearly indicated in case of e.g. a recurrence in the IMC or a positive sentinel node in the IMC. Several techniques have been described to irradiate the IMC in combination with the breast/thoracic wall, e.g. wide tangential fields, 1 AP-field with separate tangential fields for the breast/thoracic wall, or an oblique incident field, abutting tangential (half) beams. To delineate the IMC, lymphoscintigraphy or CT data have been shown to be superior to ultrasound. The above mentioned techniques will be compared with respect to CTV coverage and dose to heart and lung.

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Whole genome views on cancer

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The knowledge of the sequence of the human genome has created a nearly unlimited horizon of opportunities for study, in parallel, all human genes. Much of the challenges lie in developing new technologies as well as for the statistical and mathematical approaches necessary to interrogate the massive data that are produced. DNA microarray technology, in which the expression or copy number of genes can be determined genome-wide, offers great potential for improving our understanding of the causes and progression of disease, for the discovery of new molecular markers, for therapeutic intervention and for developing new prevention strategies. Microarray technologies, applied to the study of DNA, RNA, can be used to portray a tumor's detailed phenotype in its unique context, and to generate molecular signatures that can be correlated to clinical information. Eventually, advances in tumor portraiture will naturally lead to improved and individualized treatments for cancer patients.

We have performed expression studies and genome wide copy number analyses of more than 200 breast carcinomas and 100 ovarian carcinomas using high-density cDNA microarrays, aiming at novel tumour classification that can predict survival and treatment response. The expression patterns observed provided a remarkably distinctive molecular portrait of each tumour. The tumours could be classified into novel subtypes that were distinguished by pervasive differences in their gene expression patterns. Analyses of copy number alterations of breast tumors using the same cDNA arrays showed that at least 12% of all the variation in gene expression is directly attributable to underlying variation in gene copy number.

These findings set the stage for future studies aimed at identifying specific patterns of gene activations that predict important clinical features, like sensitivity to specific therapies and metastatic potential. Similar variation in expression of a set of genes across a set of samples indicates similar means of regulation and function, and hence, provides a powerful way of identifying novel biologically important genes that could be used as markers and targets for therapy. The strength of this method lies in the ability to identify clusters of genes that in a unique combination will distinguish subgroups of disease and predict outcome or treatment response. Such a multi-gene approach will undoubtedly be superior to standard clinical markers currently in use.

References

[1] Nature: 406, 747, 2000
[2] PNAS: 98, 10869, 2001
[3] Molecular Intervention, 2 no. 2, 101, 2002
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[5] PNAS 2003 Sørlie et al in press

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Prospective trials in rectal cancer

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Numerous prospective studies have been published about rectal cancer. In the Cochrane library 613 controlled studies and 6 complete systematic reviews are available. Most trials are concerning screening, adjuvant treatment by either radiotherapy or chemotherapy (sometimes in combination) and systemic treatment in metastatic disease. Diagnostic procedures and treatment especially surgery was not standardized in nearly all studies. This puts all the old studies mainly in an historical perspective and interpretation to the present situation should be with caution. Primary end-points are local recurrence rates and (disease free) survival. Relevant secondary endpoints are percentage stoma free survival, quality of fecal continence and both urinary and sexual function. Late sequelae of the radiotherapy are also relevant. Based on the available literature: Total Mesorectal Excision is the surgical standard, radiotherapy should be included preoperatively either as a long or a short course and the role of adjuvant chemotherapy is not yet established. All new studies should have standardized diagnostic (both imaging and pathology) and therapeutic procedures. Molecular biology will have an influence on stratification of patient groups. The standard in the control arm in primary non-metastatic rectal cancer has a local recurrence rate of 5% and a 5-year survival rate 70%. These absolute data from the control arm provides us information about the quality of the trial setup. An overview of the different trials will be given with conclusions leading to the standard treatment of primary rectal cancer. Questions that have to be solved in upcoming studies will be discussed.