WEDNESDAY 24 SEPTEMBER 2003

Teaching Lectures

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IMRT in head and neck as a model in other sites

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The purpose is to review the results of IMRT for head and neck (H&N) cancer; to analyze if toxicity and local control rates have been improved; to formulate hypothesis for improvements in the next 3-5 years and to discuss unifying principles between IMRT for H&N cancer and for other sites.

Bilateral neck IMRT was performed for oral cavity, pharyngeal and laryngeal cancer with functional sparing of salivary glands, reduction of xerostomia and without increased incidence of recurrences nearby the spared region. Low rates of recurrences were observed in elective nodal sites indicating that PTV definition and prescription doses were adequate. Recurrences were mainly located in the high dose-prescription regions (GTV, tumor bed), suggesting the need for higher doses in these regions. In sinonasal cancer, IMRT avoids dry-eye syndrome and optic neuropathy but cannot reverse the high failure rates in T4b disease. For all H&N sub-sites, planning studies show improved coverage with IMRT. In clinical IMRT studies, substantial dose escalation was not achieved and improved local control for H&N cancer seems unlikely. Progress in biological imaging, mostly based on PET, may allow us to identify recurrence-prone regions inside the GTV as targets for focused dose escalation.

Loco-regional control after radiotherapy for other tumor sites like lung, pancreas, cervix and rectum also occurs mostly in the GTV or tumor bed and not in elective lymph node sites. As for H&N cancer, further dose escalation is often prohibited by large size PTVs and image guided focused dose escalation seems applicable.

For focused dose escalation IMRT, smaller than 1 cm MLC leaf pitch and sharper than 6 mm penumbra 20-80% are needed not only in H&N. Some H&N sub-sites have air cavities and dose computation algorithms that accurately take electron non-equilibrium into account are needed during plan optimization. This is obviously also true for intra-thoracic tumor sites. With focused dose escalation, the PTV cannot be considered as spatially invariant during a long treatment course. Re-planning will be required, making image segmentation a major human effort for H&N IMRT as well as for other sites.

Conclusion: H&N cancer features most of the challenges of other tumor sites and may be considered a laboratory for further research and development including focused dose escalation IMRT.

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Integrating molecular biology in the breast cancer management

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At the present time the only molecular markers that are required for breast cancer patient management are oestrogen and progesterone receptors and HER2 (c-erbB2). Advances in understanding of molecular pathways in breast cancer have provided a cascade of new agents targeted at disrupting these. New biomarkers will be required to integrate these new therapies into patient management. To maximize the value of such biomarkers it is essential in the design of large breast cancer trials that the opportunities for defining sensitive and resistant populations are recognized at an early stage and that all efforts are made to obtain the optimal material for analysis. It is important to recognize that in adjuvant trials of breast cancer, biomarkers can define only the presence or absence of greater benefit form the treatment approaches compared: absolute and individual patient benefit cannot be established. In contrast the neoadjuvant setting allows the response of individual patients to be evaluated and the molecular characteristics of the pre-treatment tumour to be determined in relation to response. The use of expression array profiling has become popular, but the statistical limitations of this approach should be recognized. More progress may be made by targeted arrays or molecular profiling based on smaller sets of genes using such techniques as real-time PCR. New molecular markers identified by this research will require rigorous validation and establishment of rugged testing procedures to allow their integration into patient management.

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Neuroendocrine gastrointestinal tumours - diagnosis and treatment

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Neuroendocrine gastrointestinal tumors are rare neoplasms with an incidence of 1.5 – 2.0 per 100.000 inhabitants. The most common type is midgut carcinoid with an incidence of 1.0 per 100.000 followed by endocrine pancreatic tumor with an incidence of 0.5 per 100.000. A majority of patients with malignant disease present symptoms related to hormonal excess such as flushing, diarrhea, hyperglycemia, gastritis and gastric ulcers and specific skin leisons. About 30 – 40% of the patients present "non functioning tumors" and are diagnosed by intestinal obstruction, palpable liver or general signs of malignancy. The diagnosis of a neuroendocrine tumor can be verified by relevant biochemistry with Chromogranin A being the most important general tumor marker. Specific markers such as serotonin, gastrin, insulin and proinsulin can be added to the diagnostic biochemical workup. The histopathological diagnosis is very important with specific staining for neuroendocrine markers such as Chromogranin A, Synaptophysin and NSE. Besides that immunohistochemical staining for somatostatin receptors, proliferation marker, Ki 67 and growth factors might be supportive.

The localization procedure of a neuroendocrine tumor contains standard radiological procedures such as US, CT or MRI. Small endocrine pancreatic tumors can be localized by endoscopic ultrasonography. In recent year introduction of somatostatin receptors scintigraphy (Octreoscan ®) has been an important tool for localizing neuroendocrine tumors and their metastases. The staging procedure has been significantly improved by this method. About 80 – 90% of neuroendocrine tumors express somatostatin receptor type 2 and 5 which are detected by the scintigraphy. Another more experimental method is positron emission tomography (PET) using short lived isotopes such as C 11 – 5 HTP or F 18 Dopamin. The sensitivity is significantly better for PET than octreoscan and CT-scans or MRI. Treatment of neuroendocrine tumor include surgery, other cyto- reductive procedures, tumor targeted radioactive treatment, cytotoxic and biological agents.

Surgery is very important and should always be considered even in patients with malignant disease. Cytoreductive procedures include radio frequency ablation (RF) and liver emobolization/chemoembolization. Somatostatin analogue based tumor targeted radioactive treatment is still investigational but rather encouraging results have been reported with response rates of 20 – 30% in advanced cases with neuroendocrine tumors.

Cytotoxic treatment (streptozotocin + 5FU/ Doxorubicin or Cisplatinum + Etoposide have demonstrated benificial effects in patient with malignant endocrine pancreatic tumors with response rates of 50 – 60%. However low proliferating midgut carcinoids are only responding in 5 – 10% of the patients.

The biological treatment include somatostatin analogues and alfa Interferon. Octreotide is the most commonly applied somatostatin analogue with biochemical and subjective response rates of about 40 – 60% in patients with symptomatic neuroendocrine tumors. Significant tumor reduction is only noticed in about 5% of the patients. Long acting formulations of somatostatin analogues are currently in the market which has significantly improved the quality of life for patients with symptomatic tumors. Alfa Interferon has been used for treatment of malignant midgut carcinoids with biochemical and clinical response rates of about 50% with significant tumor reduction in about 10 – 15%. Both somatostatin analogues and alfa Interferon are stabilizing the tumor disease in 50 – 60% of the patients for extended periods of time (more than 36 months).