WEDNESDAY 24 SEPTEMBER 2003

Teaching Lectures

660

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.

661

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.

662

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).

The overall survival for patients with malignant carcinoids tumors and the carcinoid syndrome has increased for the last two decades from medium two years to more than nine years today. Improved diagnosis and treatment are the best explanation for this improvement.

In the future new therapies will emerge mostly based on current tumor biology including tyrosin kinase and angiogenesis inhibitors. New somatostatin analogues (som 230) are also in the pipeline for testing in neuroendocrine tumors and further development of tumor targeted radioactive treatment is ongoing. Vaccination programs are about to start and also gentherapy protocols.

663

Genetic counselling for cancer predisposition

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The availability of diagnostic molecular testing for inherited cancer calls for health care professionals to identify families at risk and to advise them of surveillance and prevention strategies. The demand for specialized Cancer Genetics Services is increasing rapidly because of heightened public awareness of genetic aspects of cancer susceptibilty and because of requests from primary care physicians for risk assessment and recommendations for appropriate management options for families with an inherited cancer susceptibility. However, the complex medical, ethical, legal and psychosocial issues brought by our ability to test healthy individuals for cancer predispositions and the rapid pace of new research findings pose great challenges to the medical community. The setup and provision of Cancer Genetics Clinics and presymptomatic Molecular Testing Services for inherited cancer as well as the education and training of health professionals involved in the provision of Cancer Genetics Services across Europe will be reviewed and issues such as how these services may best be organized and evaluated as well as the question at which level of care families at slightly, intermediately and highly elevated risk for cancer should be managed will be discussed.

664

Recording of morbidity

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All modalities employed for the treatment of the patient with cancer are associated with a risk of side effects but with most these become evident during or soon after treatment. Radiotherapy, however, differs in that the dose-limiting side effects commonly occur many months and sometimes many years after the treatment. The recording of the morbidity of treatment presents a special challenge for the

Radiation Oncologist.

The description of individual cases prevailed in the first half of this 20th-century but as we moved into the world of the randomised controlled clinical trial there was a need for a systematic approach which could be applied on an international basis. The WHO (1979) was essentially developed for the recording of the morbidity associated with cytotoxic chemotherapy but the RTOG/EORTC system for the acute and late morbidity of radiotherapy soon followed. The Franco-Italian Glossary proved valuable for the recording of morbidity due to both radiotherapy and surgery in gynaecological cancer.

All stagings were a combination of symptoms, signs, investigations and treatment and the European Dictionary was introduced in 1989 to capture the elements making up morbidity. In 1995 the LENT/SOMA was introduced as an advance on the original RTOG/EORTC in that it gave a more detailed description of the morbidity of radiotherapy with some separation of the elements making up that morbidity. In the United States the CTC version 1 (1984) built upon the original WHO was updated to version 2 in 1998 covering the sites of morbidity in much greater detail and an attempt was made to include the morbidity of all cancer treatment. In 2003 the CTC version 3 included over 500 criteria to cover all the morbidity of cancer treatment. The exact value of this system and the preceding ones needs careful consideration.

As we enter the 21st century we are aware that patients and their families have become more critical of cancer care demanding not only cure but freedom from side effects. In order to deal with this we must have accurate data as to the incidence. The complex systems required for careful assessment of morbidity in randomised controlled trials are quite unsuitable for the assessment of morbidity in the general care of all patients with cancer. Until recently this has been given very little attention now however systems are under study which may well satisfy this need.

665

Nuclear medicine in the diagnosis and treatment of paediatric tumours

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In recent years the contribution of nuclear medicine has been of increasing interest to paediatric oncology, in particular in imaging for diagnosis, staging and follow-up, in quantitative function analysis of organs at risk during oncological therapy, as well as in radionuclide therapy.

For tumour imaging a great number of tumour-seeking radiopharmaceuticals are available, exploiting various metabolic and biological properties of individual tumours; several of these agents can also be applied for radionuclide therapy. More recent tracers allow the characterization of tumours, highlighting features like hormone receptors, hypoxia, MDR and apoptosis. New techniques in paediatric oncology include PET and probe-guided surgery. A summary of applications and major indications will be presented.

Osteosarcoma/EWING's sarcoma. In differentiated osteosarcoma bone scintigraphy and SPECT using ^{99m}Tc-diphosphonate, targeting the tumour-produced osteoid, may visualize not only the primary bone tumour and skeletal metastases, but also the extraosseous metastases. For preoperative therapy and palliation of metastases beta-emitting bone-seeking agents, such as ^{89}Sr-chloride, ^{186}Re-HEDP and ^{153}Sm-EDTMP, are available.

Lymphoma. ^{67}Ga-citrate has been used for decades in the detection, staging and follow up of lymphoma, as well as for early recognition of response to therapy. ^{201}Tl-chloride scintigraphy + SPECT and PET using ^{18}F-deoxyglucose can also be used for this purpose. ^{99m}Tc-sestamibi and ^{99m}Tc-tetrofosmin are associated with p-glycoprotein, playing a role in multidrug resistance. In adults with recurrent non Hodgkin lymphoma treatment with ^{131}I- or ^{90}Y labelled anti-CD20 antibodies is highly effective.

Thyroid carcinoma. ^{201}Tl-chloride scintigraphy together with thyroglobulin assays has become a reliable alternative to the use of ^{131}I-iodide in the follow-up of differentiated thyroid carcinoma; procedure and radiation dose to the child compare favourably with that of ^{131}I. Iodine-131 maintains its role in radionuclide therapy of thyroid carcinoma. When children become involved in the family screening of MEN 2 syndromes, a variety of tracers can be used to demonstrate medullary thyroid carcinoma:

Neuroblastoma. Because of its high sensitivity and specificity, scintigraphy using ^{123}I- or ^{131}I-metaiodobenzylguanidine (MIBG) has established its role in the diagnosis, staging and follow-up of neuroblastoma. ^{131}I-MIBG is used for the treatment of this condition. Alternatively, specific targeting may be achieved using radiolabelled peptides (e.g. ^{111}In-pentetreotide) or monoclonal antibodies (e.g. 3F8, UJ13A, BW575/9, ch14.18 and chCE7). PET using ^{18}F-deoxyglucose (FDG) and ^{11}C-hydroxyephedrin (HED) is used to image neuroblastoma and ^{124}I-MIBG and -3F8 antibodies for dosimetry prior to therapy.

Rhabdomyosarcoma. Aspecific tracers, e.g. ^{67}Ga-citrate, ^{201}Tl-chloride and ^{18}F-deoxyglucose, can be used to image rhabdomyosarcoma. An example of specific targeting of rhabdomyosarcoma is radioimmunoscintigraphy using ^{111}In antimyosin Fab fragments, but these are no longer commercially available.

666

Will oral drug replace IV treatment?

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Unlike most therapeutic areas where oral treatment is standard, in oncology most drugs are given intravenously. Encouraging clinical trial results indicate that for first time many of the orals anti-cancer drugs in development are better drugs rather than pale imitations of i.v. treatments. The oral route is appropriate for schedule dependent cytotoxics e.g. fluoropyrimidines as well as novel agents including signal transduction inhibitors and anti-angiogenic agents in order to achieve prolonged exposure.

Although more than 20 cytotoxics are available orally, many such as cyclophosphamide, etoposide and topotecan are also given i.v. Currently, probably the widest use of oral chemotherapy is 6-mercaptopurine, methotrexate and busulphan in leukaemias and lymphoma. Temozolamide (for glioma, astrocytoma and melanoma) and idarubicin (principally for leukaemia) are also well established but again have had limited impact as these are not the commonest cancers. 5-fluorouracil (5-FU) is, however, widely used and oral alternatives have been developed including pro-drugs that are absorbed unchanged (capecitabine, tegafur), the addition of inhibitors of the enzyme DPD that catabolizes 5-FU (uracil, eniluracil), or a combination of the two (UFT, S1, emitefur). With capecitabine now approved in