Abstracts of Invited Lectures

O-001

Direct Myocardial Ischemia Imaging

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Abstract not available.

O-002

Assessment of Myocardial Viability by SPECT

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Patients with severe coronary artery disease and left ventricular (LV) dysfunction who have undergone medical therapy, in general, have poor outcomes. Those patients who have undergone coronary revascularization have better long-term outcome, and approximately one-third of them have improved LV function after coronary revascularization. Nevertheless, because of high perioperative mortality in such patients, coronary revascularization can only be performed in selected patients who may benefit most from coronary revascularization. It is well known that the recovery of LV function after coronary revascularization is likely to occur in patients whose LV dysfunction is due to myocardial hibernation rather than irreversible myocardial damage. The advent of imaging techniques for the detection of myocardial viability has significant impact on the management of patients with ischemic Cardiomyopathy. Metabolic measurement by positron emission tomography (PET) may be the most sensitive noninvasive approach for the evaluation of myocardial viability, but its limited availability and high cost limit its broader clinical use. Experimental studies have demonstrated that myocardial uptake of TI-201, Tc-99m-labeled sestamibi or tetrofosmin is a reliable marker of myocardial viability. TI-201 myocardial imaging with one of several proposed modified protocols is relatively reliable and clinically available. The value of resting Tc-99m labeled sestamibi or tetrofosmin myocardial imaging for assessment of myocardial viability is still controversial. Recently, single-photon emitting agents in combination with nitrates have been utilized for evaluation of myocardial viability. TI-201, Tc-99m-sestamibi or Tc-99m-tetrofosmin myocardial imaging with nitrates seem to be more sensitive for detection of defect reversibility in comparison to the other TI-201, Tc-99m-sestamibi or Tc-99m-tetrofosmin imaging protocols. TI-201 Imaging: Previous studies have shown that stress, standard 3-4 hours redistribution TI-201 imaging significantly underestimates ischemic but viable myocardium. Reinjection imaging following injection of a second dose of TI-201 (1 mCi) after 3-4 hours redistribution imaging significantly improves the detection of reversible TI-201 defects, and enhances the detection of ischemic but viable myocardium. Another option is rest/redistribution TI-201 imaging, which seems to be reasonable for the detection of myocardial viability in patients with severe LV dysfunction, where myocardial viability rather than stress-induced myocardial ischemia is the major concern. Sensitivity of stress-redistribution-reinjection TI-201 imaging was high and ranged from 80% to 100%, its specificity was relatively low, and ranged from 38% to 80% for the detection of improved regional LV contractile function after coronary revascularization. Sensitivity of rest-redistribution TI-201 imaging ranged from 44% to 100%, and its specificity ranged from 22% to 92%. TI-201 myocardial imaging is a widely available and fairly reliable technique for clinical detection of myocardial viability. Tc-99m-sestamibi Imaging: Experimental laboratory studies have validated the use of Tc-99m sestamibi as perfusion as well as viability agent. Recent data shows excellent correlation between the extent and severity of myocardial scarring measured by pathology and Tc-99m sestamibi infarct size in excised hearts of patients undergoing cardiac transplantation. Some clinical studies have however demonstrated that not only qualitative but also quantitative stress/rest Tc-99m-sestamibi imaging significantly underestimates myocardial viability. In contrast, more recent studies suggest that the identification of reversible and viable myocardium can be greatly enhanced with Tc-99m sestamibi imaging if an additional redistribution imaging is acquired after rest injection of Tc-99m sestamibi, or if the severity of reduction in Tc-99m sestamibi activity within hypoperfused myocardium is considered. Previous studies reported a high sensitivity of Tc-99m-sestamibi, whereas specificity varied from 35% to 86%. Tc-99m-tetrofosmin imaging: Although the diagnostic value of Tc-99m-tetrofosmin myocardial imaging has been established, thus far, little information is available on accuracy of Tc-99m-tetrofosmin imaging for assessment of myocardial viability. Matsunari et al demonstrated that visual analysis of exercise-rest tetrofosmin imaging might underestimate the detection of myocardial viability as compared with TI-201 reinjection imaging. On the other hand, quantitative analysis of TI-201 and
tetrofosmin uptake within irreversible defects provided similar information. Recent study by Nicolai et al showed that TI-201 and tetrofosmin activity is comparable in normokinetic and hypokinetic myocardium. However, in segments with severe LV dysfunction, tetrofosmin myocardial uptake at rest was lower as compared with both redistribution and reinjection images. However, no functional data were reported in the above studies. Nitrate-augmented myocardial imaging: We and other investigators have evaluated effects of nitrates on the detection of defect reversibility by myocardial perfusion imaging with Tl-201 or Tc-99m labelled sestamibi or tetrofosmin. The results are consistent in showing that nitrates improve the detection of defect reversibility. Several studies have evaluated the accuracy of nitrate-augmented myocardial imaging for prediction of recovery of LV regional contractility. Overall, nitrate-augmented TI-201 or Tc-99m-sestamibi imaging has a high sensitivity and specificity. According to the published data, sensitivity and specificity of nitrate-augmented Tc-99m-sestamibi imaging ranged from 82% to 95%, and from 76% to 89% respectively. Overall, nitrate-augmented TI-201 or Tc-99m-sestamibi imaging has a high sensitivity and specificity. We and other investigators have recently evaluated its prognostic value. Therefore, at present, the results seem the best using nitrate-augmented conventional radionuclide myocardial imaging. Because the administration of nitrates is simple and inexpensive, unless contraindicated, they should be administered before administration of TI-201, Tc-99m sestamibi or Tc-99m tetrofosmin when the main purpose of the study is assessment of myocardial viability.

FDG SPECT imaging: With the recent development of SPECT imaging, myocardial FDG metabolism imaging can be performed with SPECT equipped with ultra-high energy collimator or SPECT with coincidence detection. Several studies have demonstrated a good agreement between FDG PET and FDG SPECT for the evaluation of myocardial viability. Recent studies have reported the predictive value of FDG SPECT for prediction of the recovery of LV function after coronary revascularization. Simultaneous assessment of myocardial perfusion and viability can be performed with dual isotope simultaneous acquisition technique. This novel technique warrants further studies.

O-006

Myocardial Perfusion Imaging as a Gatekeeper for Coronary Angiography

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Nuclear cardiology has developed into an extremely valuable tool for diagnosis and risk stratification of coronary artery disease. As clinical symptoms, baseline and stress ECG have low sensitivity and specificity, physicians and cardiologists require non-invasive techniques to detect and prognosticate patients with ischemic heart disease. Myocardial perfusion imaging (MPI) achieves great accuracy in the diagnosis of the disease and in identifying the patients with higher risk for adverse events. Literature shows that it is not the coronary anatomy but the ischemic burden that determines prognosis in patients with ischemic heart disease. Patients with normal MPI, independent of age, gender, and symptoms, history of coronary artery disease, presence of anatomic coronary artery disease (CAD) or isotope or imaging technique, have a <1% risk of adverse events (myocardial infarction or cardiac death) for a period of at least 12 months. ECG changes, post-stress left ventricular dilatation, increased tracer uptake by the lungs, drop in left ventricular ejection fraction from rest to stress are non-perfusion markers of severity. Left ventricular function, regional wall motion abnormalities as well as myocardial viability can be evaluated with MPI.

O-007

Myocardial Perfusion and Viability by Cardiac CT, MR and ECHO

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The importance of myocardial perfusion and viability in the treatment of ischemic heart disease is very well documented and accepted. The accurate assessment of such indices helps select patients with coronary artery disease who will benefit from revascularization therapy, medical therapy or new novel therapies. The role of nuclear perfusion and viability assessment is undeniable. More recently, other modalities have emerged in such assessment, mainly because of the realization that such data is crucial in determining treatment modalities.

Cardiac CT: This new modality has come into prominence in recent years. The role of contrast cardiac CT in determination of perfusion and viability stem from

O-003

Nuclear Medicine in Heart Failure

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Abstract not available.
the fact that contrast will perfuse the microcirculation of the myocardium, thus enhancing the myocardial intensity during imaging. The amount of enhancement is directly proportional to the amount of contrast flow into the microcirculation, thus reflecting the adequacy of coronary circulation. The timing of such a “perfusion image” is vital, as this myocardial contrast enhancement only occurs over a short window of time after contrast injection. Viability by contrast CT is also possible, usually by acquiring another cardiac image about 6 to 8 minutes after the initial contrast CT scan. In this case, the pooling of iodinated contrast in the non-viable myocardium will show hyper-enhancement in the region of infarcted myocardium, akin to the hyper-enhancement seen with gadolinium-enhanced cardiac MR.

**Cardiac MR:** The use of gadolinium enhancement of cardiac MR has made it possible to assess both myocardial perfusion and viability. With principles similar to cardiac CT, early dynamic cardiac MR after gadolinium injection will be able to show perfusion of the myocardium by enhancement, whilst late hyper-enhancement after gadolinium injection represent infarcted myocardium as gadolinium is pools into areas of fibrosis with increased free water deposition. This technique of viability assessment has been touted as the “gold standard” for myocardial viability assessment.

**Echocardiography:** Echocardiography has been widely used in cardiology, both in the detection of structural heart disease and also for assessment of wall motion and viability. The presence of thinned out akinetic myocardium usually signify non-viable myocardium. However, this technique is less sensitive as compared to cardiac MR and CT in detecting viability. The addition of low dose dobutamine infusion during wall motion assessment by echocardiography can improve the assessment of viability, represented by improved wall motion scores during such infusion. When dobutamine is infused in incrementally higher doses, the detection of worsening wall motion is a sign of myocardial ischemia, attesting to the presence of perfusion deficits in the coronary circulation. Low dose dobutamine assessment of myocardial viability is less sensitive but more specific compared to other imaging modalities like nuclear imaging.

The new technique of contrast echocardiography has vastly improved the detection of both perfusion and myocardial viability, in addition to improving the overall accuracy of detection of wall motion abnormalities. The use of contrast significantly improves the delineation of cavity from myocardium, thus improving the wall motion abnormality detection. In addition, contrast can be traced in the myocardium itself as it perfuse the microcirculation, thus improving the visualization of a relative lack of contrast in areas of perfusion deficits, and also an absence of contrast opacification in areas of myocardial infarction. Thus in 2011 there are many new techniques competing for the perfusion/viability detection pie. It is important the nuclear imaging keep up with such competing techniques, in terms of accuracy of detection, cost effectiveness, ease of use and availability.

**O-008**

**Multimodality Assessment of Myocardial Ischemia and Viability - Positron Emission Tomography and Single Photon Emission Computed Tomography**

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Positron emission tomography (PET) and single photon emission computed tomography (SPECT) provide molecular orientation of biomedical processes and computed tomography (CT) provides anatomical orientation through beautiful images especially when they are combined. Introduction of PET can be traced early 1940s, however, application of PET/CTand SPECT/CT to clinical practice became only recently popular. Majority of clinical application of PET/CT is for oncology patients while clinical application of SPECT/CT can be wider than PET/CT.

In the field of cardiovascular medicine PET is combined with tracer kinetic modeling to measure regional myocardial blood flow (MBF). It is useful to evaluate microvascular circulation of myocardium. Convenient production of rubidium-82 from generator accelerated use of cardiac PET in North America. Recently Rb-82 generator is using in Europe and in some part of Asia. Conventional radiotracers for myocardial perfusion include nitrogen-13 (N-13) ammonia, oxygen-15 (O-15) water, carbon-11 (C-11) butanol and copper-62 (Cu-62) PTSM. Recently fluorine-18 (F-18) labeled myocardial perfusion agents are developed and tested. Unraveling coronary circulatory function can be possible using those radiotracers by pharmacologic vasodilation, sympathetic stimulation with cold water, or adrenergic stimulation. Measurement of MBF using PET makes understanding of early stages of coronary artery disease (CAD) and therefore development of new drugs possible.

**Imaging of cardiac autonomic nervous system had advanced using iodine-123 (I-123) metaiodobenzylguanidine.** Recently various PET tracers for pre- and postsynaptic binding have been introduced. Tracers for presynaptic sympathetic imaging include C-11 hydroxyephedrine, C-11 epinephrine, C-11 phenylephrine, and F-18 fluorodopamine. Those for postsynaptic sympathetic imaging include C-11 CGP12177, C-11 CGP12388, and C-11 GB67. Tracers for myocardial metabolism include F-18 fluorodeoxyglucose for glucose metabolism, C-11 acetate for oxygen metabolism, C-11 palmitate and
F-18 FTHA for fatty acid metabolism, and C-11 lactate for lactate metabolism. I-123 BMIPP can be used for fatty acid metabolism. They can be used for assessment of pathophysiologic process of myocardial ischemia including viability.

Recent clinical application of cardiac PET and PET/CT include measurement of MBF and flow reserve, coronary endothelial function, monitoring responses to therapeutic intervention, evaluation of myocardial viability and ischemic memory, and detection of inflammatory plaques. Cardiac CT gives information on coronary artery calcium plaque burden as well as morphology coronary arteries. Low specificity of CT coronary angiography (CTCA) can be overcome by adding perfusion information by PET or SPECT. Hybrid imaging of PET/CT can pinpoint culprit or target lesions for revascularization in case of multivessel coronary disease. It also can show inflammatory plaques in great vessels, which are associated with increased risk of cerebral embolic infarction. Radiation burden is one of concerns in hybrid imaging, which can be alleviated by recent development of low dose imaging protocols.

O-009

Radioiodine Treatment of Differentiated Thyroid Carcinoma: Experience in Seoul National University Hospital

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After specific accumulation of iodide in the thyroid gland was found, radioactive iodine therapy has been important role in the treatment for differentiated thyroid cancer. In addition, the incidence of thyroid cancer is increasing in many countries including Korea. Conventional I-131 therapy has effect on the treatment of metastatic thyroid cancer. To get effect of I-131 therapy, tumor should accumulate iodide uptake. However, about 20-30% of thyroid cancer do not accumulate iodide and shows poor prognosis comparing with differentiated thyroid cancer. For such cases, there are several methods to increase the effect of radio active iodine therapy. One could be increasing the administration dose within maximal safe dose to increase the delivery of I-131 to tumor. The other could be using retinoic acid to induce re-differentiation of cancer cell and to restore the accumulation of iodide in cancer cells. By such efforts, the clinical outcome of thyroid cancer was improved. Historically, radioiodine treatment was started in Seoul National University Hospital. “Radioisotope Clinic” was open in 1960 in this hospital and has had in the central role of nuclear medicine in Korea. In this paper, we summarized the data and experience of I-131 treatment on recurrent/metastasis of DTC in Seoul National University Hospital.

O-010

Thyroid Cancer and the Benefit of rhTSH in Treatment

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Differentiated thyroid carcinomas (DTC) are an unusual disease with a good prognosis, but the incidence rose since 1973 to about 50%. In Germany new thyroid cancer are diagnosed in a frequency of about 30 in 1 million people per year, but the death rate is low with 5 deaths in 1 million people per year. The DTC are divided in papillary thyroid cancer (typically frequent in 15 to 35 years and lymphogenic metastases) and follicular thyroid cancer (sporadic > 20 years, frequent in elderly patients and metastases via blood). The age is a significant factor in recurrence-free survival; younger age is a good prognostic factor. A special form is the papillary microcarcinoma with an excellent recurrence-free survival; tumors with a size > 5mm showed only in 3% a recurrence within 35 years after diagnosis and a size 6-10mm had recurrence-free survival in 86%. However, own experiences showed also patients with papillary microcarcinoma and lymph node metastases at primary diagnosis.

Typically treatment scheme is the surgical total ablation of thyroid following a radioiodine ablation using 3.7 GBq of \textsuperscript{131}I. The patients should have an iodine scan in the hypothyroid state (TSH level > 30) 4-6 months after radioablation to control the treatment and exclude lymph node and distant metastases. Before radioablation the sensitivity of iodine scan is significant lower than after total ablation, the normal thyroid cell has a higher uptake of iodine than the thyroid cancer cell. The follow-up schema is different in low-risk patients (T\textsubscript{1} and T\textsubscript{y} N\textsubscript{0}, M\textsubscript{0}) and high-risk patients (all other tumor stage) in our department. Low risk patients have an iodine scan 1, 5 and 10 years after primary diagnosis and a yearly ultrasound and thyroglobulin (TG) control. High-risk patients underwent an iodine scan 1, 3, 5 and 10 years after primary diagnosis and a half-yearly ultrasound and TG-control.

Treatment and follow-up scans with iodine should
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be performed under adequately stimulated TSH level (> 30 mU/l) to optimize the iodine uptake by stimulation of the sodium-iodide-symporter. There are two options for TSH stimulation, withdrawal of thyroid hormone or alternative administration of recombinant human TSH (rhTSH). For withdrawing hormones, the patients discontinued the thyroxin (T4) for 8 weeks and replace by triiodothyronine (T3). The T3 should be stopped 10 days before iodine administration. This way is cheap but some patients have severe side effects, such as fatigue, increase of body weight, reduce vitality and social function. Some patients are incapacitated for work. The rate of side effects for rhTSH administration is significant lower and includes e.g. nausea, vomiting and headache. The rise of TSH is similar in cases with withdrawal of hormones or rhTSH administration. A disadvantage of rhTSH is the high costs for the drug. RhTSH is approved for radioiodine ablation, whole body scan using radioiodine and stimulated TG-screening, in our department we use rhTSH also for the therapy of metastases.

DTC is an unusual tumor with good prognosis, slow growth and low rate of metastases. The iodine therapy allows a specific treatment of thyroid cancer cells if the sodium-iodide-symporter is expressed. For optimal condition for treatment or whole body iodine scan the patient should have a TSH > 30mU/l. For this condition rhTSH is an effective option with low rate of side effects compared to withdrawal of hormones.

0-011

Radioiodine Non-avid Thyroid Cancer - What is New?

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Radioiodine non-avid thyroid cancer (TC) is a rare disease entity with a poor prognosis. Despite a multimodal therapeutic approach including surgery, chemotherapy and external beam radiation, radioiodine non-avid TC accounts for a high number of TC associated deaths and poses a therapeutic challenge in clinical routine. Furthermore, the long-term survival rate in patients with radioiodine non-avid TC declines to 10%. Among these patients, the ones who show high tracer uptake in [(18) F] 2-deoxy-2-fluoro-D-glucose positron emission tomography ([18]F-FDG PET) carry a particularly poor prognosis. It is well known that [18]F-FDG PET is an effective imaging modality in the postoperative management of patients with TC, particularly in patients with elevated serum thyroglobulin (TG) levels and Iodine-131 (I-131) scans without pathologic uptake, indicating a more aggressive type of disease. One of the main limiting factors in these patients is the low response rate to chemotherapy or external beam radiation with a relatively high risk of serious adverse events. Thus, chemotherapy is generally reserved for patients with rapidly progressive disease or symptomatic metastatic disease, unresponsive to surgery, external beam radiation and radioiodine. As there has been significant progress regarding the targeting aberrant signalling pathways of tumor cells, the clinical benefit of various target-specific therapeutic agents has been investigated in these tumors. In our institution, one option for patients with signs of disease progression is based on the selection of tumors with high somatostatin9-receptor (SSTR) expression. 68Ga-DOTA-TOC PET is performed to select patients with high SSTR expression for peptidereceptorradionuclide therapy (PRRT), if they are refractory to conventional treatment modalities. Target-specific anticancer agents such as sorafenib and sunitinib have already been tested with some success, and were therefore included into the practice guidelines for metastatic TC. The National Comprehensive Cancer Center Network (NCCN) Guidelines in Oncology currently recommend consideration of small-molecule kinase inhibitors in patients with progressive metastatic TC. Recently, antitumoral activity of bortezomib in TC cells has been demonstrated in vitro. Bortezomib is a proteasome inhibitor with known NF{kappa}B inhibitory activity. Bortezomib stimulates the release of proapoptotic proteins, reduces the activity of antiapoptotic proteins and enforces the formation of reactive oxygen species. In addition, it induces an endoplasmatic reticulum (ER) stress reaction. Our recent data indicate that the proteasome inhibitor bortezomib may be used for the treatment of patients with progressive undifferentiated TC and good performance status to inhibit further tumor progression and maintaining or improving quality of life.

Figure : Management strategy for I-131 negative and FDG positive thyroid cancer
O-012

Eurasian Federation of Oncology: Ventures for Collaboration with WARMTH

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Abstract not available.

O-015

Thyroid Cancer - State of the Art

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State of Art is the highest level of development, as of a device, technique, or scientific field, achieved at a particular time. We are trying to explore in this presentation, if dealing with Thyroid Cancer, meet the criteria of “State of Art”.

Thyroid Nodules Management: Thyroid nodules are a common problem in the population. The prevalence of palpable thyroid nodules is approximately 5% in women and 1% in men living in iodine-sufficient parts of the world. On the other side high-resolution ultrasound (US) can detect thyroid nodules in 19–67% of randomly selected individuals with higher frequency in women and the elderly. Having in mind the large number of people with palpable nodules in Thyroid and the small number of Patient with Thyroid cancer is a need of a detail evaluation of these people trying to find out who needs an operation. Nodules less than 1 cm should not be evaluated except if they have suspicious US findings, associated lymphadenopathy, a history of head and neck irradiation, or a history of thyroid cancer in one or more first-degree relatives.

Patient having an incidental finding on PET showing increase uptake in Thyroid nodule should be evaluated due to the fact that the risk of malignancy is about 33%. A key role in evaluation is Ultrasonography (U/S), TSH measurement, Thyroid scintigraphy and Fine Needle Aspiration (FNA)

U/S should give the following answers: Is there truly a nodule that corresponds to the palpable abnormality? How large is the nodule? Does the nodule have benign or suspicious features? Is suspicious cervical lymphadenopathy present? Is the nodule greater than 50% cystic? Is the nodule located posteriorly in the thyroid gland?

TSH measurement plays an important role in the evaluation. If suppress or subnormal, thyroid scintigraphy should be done. Hot nodules rarely harbour malignancy, Cold nodules needs further evaluation with FNA. If TSH is higher this is associated with increased risk of malignancy in a thyroid nodule.

FNA (without or with U/S guidance) is an important tool in the evaluation of suspicious Thyroid Nodules. The results determinate the further management. If Benign: further immediate diagnostic studies or treatment are not routinely required, but follow-up is require because of a false-negative rate of up to 5% with FNA. If there is 20% increase in nodule diameter with a minimum increase in two or more dimensions of at least 2mm we should repeat FNA.

Indeterminate cytology, (e.g. follicular neoplasm, Hurthle cell neoplasm, follicular lesion of undetermined significance, atypia) bear a risk of malignancy about 20 to 30%. In that case we could use molecular markers (BRAF, RAS, RET=PTC, Pax8-PPARG, galectin-3). 18FDG-PET could be for help or we can repeat FNA Biopsy in 6 months. If FNA shows Suspicious for Malignancy (risk of Thyroid Cancer 50-75%) or Malignant (100%) Surgery is indicated. Before Surgery a preoperative staging is important. Preoperative neck US for the contralateral lobe, searching for Cervical (central and especially lateral neck compartments) suspicious lymph nodes and U/S guided FNA of sonographically suspicious lymph nodes should be performed to confirm malignancy.

Thyroid Surgery: Thyroid surgery include Hemithyroidectomy (with or without isthmusectomy), near-total thyroidectomy (removal of all grossly visible thyroid tissue, leaving only a small amount [<1g] of tissue adjacent to the recurrent laryngeal nerve near the ligament of Berry), total thyroidectomy (removal of all grossly visible thyroid tissue). The extent of surgery depends on the preoperative staging and FNA results: hemithyroidectomy should apply in an isolated indeterminate solitary nodule but if the Nodule is more than 4cm or it is marked atypia on biopsy or family history of thyroid carcinoma or there is history of radiation exposure or bilateral nodular disease or the patient wish to avoid future surgery. On those cases near total or total thyroidectomy should apply.

In the rest of the cases also near total or total thyroidectomy should apply. Important, regarding the extent of the surgery, is the question if Central Neck Dissection should be performed. The central neck dissection, could be bilateral: Removal of the prelaryngeal, pretracheal, and both the right and left paratracheal nodal basins or unilateral: Removal of the prelaryngeal, pretracheal, and one paratracheal nodal basin. A therapeutic central compartment neck dissection implies that nodal metastasis is apparent clinically (preoperatively or intraoperatively) or by imaging (clinically N1a). A prophylactic/elective central compartment dissection
implies nodal metastasis is not detected clinically or by imaging (clinically N0). Central neck dissection should be considered in light of available surgical expertise. For patients with small, noninvasive, apparently node-negative tumors, the balance of risk and benefit may favor simple near-total thyroidectomy with close intraoperative inspection of the central compartment with compartmental dissection only in the presence of obviously involved lymph nodes. This approach may increase the chance of future locoregional recurrence, but overall this approach may be safer in less experienced surgical hands.

Postoperative Risk Classification of Thyroid Cancer Patients: Low risk: no local or distant metastases; all macroscopic tumor has been resected; there is no tumor invasion of loco-regional tissues or structures; the tumor does not have aggressive histology (e.g., tall cell, insular, columnar cell carcinoma) or vascular invasion; and, if 131I is given, there is no 131I uptake outside the thyroid bed on the first post-treatment whole-body RAI scan
Intermediate Risk: microscopic invasion of tumor into the perithyroidal soft tissues at initial surgery; cervical lymph node metastases or 131I uptake outside the thyroid bed on the post-treatment whole-body RAI scan done after thyroid remnant ablation; tumor with aggressive histology or vascular invasion
High-Risk: macroscopic tumor invasion; incomplete tumor resection; distant metastases; thyroglobulinemia out of proportion to what is seen on the post-treatment scan.

Ablation Therapy: The discussion about the necessity of ablation therapy in low risk patient is long but in generally ablation is not recommended for patients with unifocal cancer <1 cm without other higher risk features. The amount of dose which should be given is also part of long discussions. Dose between 30mCi and 150mCi are recommended for ablation Therapy. The post-therapy scan is in all cases helpful in the staging of the patient (extrathyroidal spread) and SPECT/CT can ad on value.

Therapy of Advance Thyroid Cancer: In the setting of advanced disease, 131I therapeutic activities ideally should be chosen with the goal of delivering to all tumor foci the highest reasonable absorbed dose. The minimum absorbed dose needed to destroy DTC metastases is believed to be 100 Gy. Therapeutic activities should also be chosen so as to avoid exceeding a blood dose of 2 Gy a threshold considered as a surrogate for bone marrow toxicity. In clinical applications, the pre-therapy 124I-PET dosimetry may result in a significant alteration in the therapeutic procedure compared to standard therapy using fixed therapeutic activities. TSH Suppression Therapy: High and Intermediate risk patients TSH suppression should be less than 0.1mU/L and in Low risk patients with or without ablation therapy TSH suppression between 0.1 and 0.5mU/L.

Management of Tg-positive, RAI Scan-negative Patients: Neck Ultrasound, CT Thorax (without contrast) MRI neck and mediastinum (especially in patient with N1 status) and if Tg is more than 10ng/ml (T4 withdrawal) or more than 5ng/ml rhTSH stimulation or is rising Tg then empiric dose of (100-200mCi)Iodine-131 for therapy should be used. When the whole body scan after empiric I-131 therapy is negative FDG-PET scan is indicated. Some authors suggest to perform FDG-PET before I-131 therapy since FDG positive tumor do not concentrate Iodine to avoid unnecessary I-131 therapy. Patient with Tg positive, post Therapy Scan NEGATIVE disease incurable with surgery and FDG-PET positive findings should treated with T4 suppression therapy, external beam radiation or chemotherapy.

Future research: A minority of the patient, who will not benefit of surgery and I-131 therapy, can experience progressive life threatening growth and metastatic spread of the disease. For these patients a range of targeted therapies are undergoing clinical evaluation. (Inhibitors of oncogenic signaling pathways; Modulators of growth or apoptosis; Angiogenesis inhibitors; Immunomodulators; Gene therapy)

Risk Stratification: Current risk stratification schemes rely almost exclusively on clinical, pathological, and radiological data obtained during the initial evaluation and therapy of the patient A risk stratification system that incorporates all the important information available at presentation and also evolves over time as new data become available would be useful in providing ongoing risk assessments that would optimize management throughout the life of the patient.

Conclusion: While surgery and the use of Iodine-131 therapy, is sufficient treatment for the majority of patients with Differentiated Thyroid Cancer, a minority of these patients experience progressive, life-threatening growth and metastatic spread of the disease. We need to find out the group of those patients and explore the possibility to give them the best treatment.
many published consensus reports, the most important are: the American Thyroid Association’s guidelines for patients with thyroid nodules and differentiated thyroid cancer, European consensus for the management of patients with differentiated thyroid carcinoma of the follicular epithelium and EANM guidelines for radioiodine therapy of differentiated thyroid cancer. According to the ATA guidelines, the main goals of initial therapy of DTC are: to remove the primary tumor, disease that has extended beyond the thyroid capsule, and involved cervical lymph nodes; to minimize treatment-related morbidity; to permit accurate staging of the disease; to facilitate postoperative treatment with radioactive iodine; to permit accurate long-term monitoring for disease recurrence; and to minimize the risk of disease recurrence and metastatic spread. According to both, the European consensus and ATA guidelines, apart from unifocal, intrathyroidal, well DTC less than 1cm in diameter with no evidence for nodal or distant metastases and no history of previous radiation exposure that may be operated on less than total thyroidectomy, the standard surgical treatment is total (or near-total) thyroidectomy, which decreases the risk of local recurrence, facilitates postsurgical radioiodine ablation and adequate follow-up. Compartment-oriented microdissection of lymph nodes should be performed in cases of preoperative suspected and/or intraoperatively proven lymph node metastases. The radical surgery has a favourable impact on survival in high-risk patients, and on the recurrence rate in low-risk patients. The benefits of prophylactic “en bloc” central node dissection in the absence of pre- or intra-operative evidence for nodal disease are still controversial. However, ATA recommends that prophylactic central compartment neck dissection (ipsilateral or bilateral) may be performed in patients with papillary thyroid carcinoma with clinically involved central neck lymph nodes, especially for advanced primary tumors (T3 or T4). They also recommend that near-total or total thyroidectomy without prophylactic central neck dissection may be appropriate for small (T1 or T2), non-invasive, clinically node-negative papillary and most follicular cancer. Therapeutic lateral neck compartmental lymph node dissection should be performed for patients with biopsy-proven metastatic lateral cervical lymphadenopathy. Postoperative staging allows risk stratification on individual patients, which will dictate the frequency and type of follow-up. There are several prognostic scoring systems, but the most popular is AJCC/UICC staging because of its utility in predicting disease mortality and its requirement for cancer registries. In accordance with this system, the patients are grouped into three risk categories at the time of initial treatment: very low risk including unifocal T1 (≤1cm) N0M0 and no extension beyond the thyroid capsule; low risk including T1 (>1cm) N0M0 or T2N0M0 or multifocal T1N0M0; and high risk including any T3 and T4 or any T,N1 or any M1. Radioiodine ablation is not recommended for very low risk patients, but is definitely recommended for high risk patients. There is no consensus regarding the ablation for low risk group. ATA suggest that ablation is not recommended for patients with multifocal cancer if foci are <1cm in the absence of other high risk features. On the other hand, EANM guidelines suggests that radioiodine ablation after total or near-total thyroidectomy is a standard procedure in DTC patients, with exception of patients with unifocal PTC >1cm in diameter who lack evidence of metastasis, history of radiation exposure and unfavourable histology (papillary tall-cell, columnar cell or diffuse sclerosing subtypes). In these cases, complete thyroidectomy is not the rule and radioiodine ablation is not indicated. However, if total thyroidectomy is performed, ablation should be considered by means of improving follow-up and decreasing the recurrence rate. EANM guidelines also recommends to evaluate the ablation success after 6-12 months after the ablation procedure by performing the following criteria: on follow-up dx WBS, negative thyroid bed uptake or thyroid bed uptake < 0.1%; absence of detectable Tg when interference by anti-Tg antibodies has been excluded; and absence of suspicious finding on neck ultrasonography. There are also differences according to the activity of 131I given for ablation therapy. American Society of nuclear medicine procedure guidelines for therapy of thyroid disease with Iodine-131 suggests for postoperative ablation of thyroid bed remnant activity in the range of 2.75–5.5 GBq, depending on the RAIU and amount of residual functioning tissue present. According to the EANM guidelines, empirically determined and fixed activities are given usually in a range between 1.11 GBq to 3.7 GBq. Recent published studies concluded that current evidence cannot yet confirm about the ablation success rates between performed activities of 1.11 GBq versus 3.7 GBq. In children, the adjustment the activity by body weight or surface area or by age is necessary. Inoperable iodine-avid metastases in adults are treated with multiple iodine treatments, each 3.7 GBq to 7.4 GBq or more, given every 4-8 months during the first two years following the diagnosis of metastatic disease and at longer intervals thereafter. As an alternative to the fixed radioiodine activites pre-therapeutic dosimetry may be used to measure an individualized activity projected to deliver a desired amount of radioactivity to tumor or extra-thyroidal compartments, or both. The generally accepted absorbed dose thresholds providing high efficacy
are ≥300 Gy to remnants or ≥80 Gy to tumor deposits. The generally accepted surrogate dose threshold to avoid serious myelotoxicity is a blood absorbed dose ≤ 2 Gy. Radioiodine treatments should continue until there is no longer evidence of metastatic disease or until there is no longer radioiodine uptake on rx WBS. There is no maximum limit for the cumulative I-131 activity that can be given to patients with persistent iodine-avid disease. In most cases, remissions are achieved with cumulative activities ≤22 GBq; above this threshold, further radioiodine therapy should be considered on an individual basis.

Summary: Treatment protocols for DTC vary from country to country, however it is important to implement a uniform treatment strategies since the disease requires multidisciplinary approach. Radioiodine therapy is an useful adjunct for DTC treatment, it prolongs life and improves quality of life. Differentiated thyroid carcinoma patients needs life-long follow-up.

O-017

Radioiodine Treatment of Hyperthyroidism-A Review

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The use of I-131 in 1946 for the treatment of hyperthyroidism marked a historic event. It ushered in a new era of radionuclides in medicine and led to the birth of nuclear medicine. Today I- 131 has become one of the most commonly used agents and best option for the treatment of hyperthyroidism.

Hyperthyroidism is a hypermetabolic state induced by excess of thyroid hormone. It can develop secondary to thyroid hormone released from an overactive or inflamed thyroid gland or from an extraglandular source. Predisposing factors include the following: Autoimmunity, genetic susceptibility to the disease, stressful life events, infection (thyroiditides) and recent childbirth (postpartum-2 to 6 months). Other causes could be thyrotoxic factitia, iodine excess, amiodarone intake, pituitary tumors, struma ovari and metastastic thyroid cancer. There are numerous causes but Graves’ disease is the most common cause. Since thyrotoxicosis is a component of many syndromes, treatment depends on the cause and severity of the disease.

The most useful diagnostic test is a decreased TSH level. Other laboratory findings will show elevated FT4 and FT3. To rule out other causes, a RAIU and scan can be done which will show the functional anatomy and elevated uptakes. Antithyroid peroxidase antibodies (ATPO), antithyroglobulin antibodies, TRAB can differentiate Hashimoto’s thyroiditis from Graves as well as monitor response to antithyroid treatment. Treatment includes: Antithyroids which block new hormone synthesis and release usually indicated for children and young adults; pregnant and lactating mothers; mild hyperthyroidism and small goiters and as pretreatment for elderly prior to RAI

More definitive treatment includes I-131 for ablation of thyroid tissues indicated for older patients, for recurrent hyperthyroidism and relapse after surgery, those with accompanying serious illness and those allergic to drugs; and surgical-for big bulky goiters causing obstruction and those with co-existent cancers.

Radioactive iodine is indicated in the treatment of Graves’ disease, toxic multinodular goiter, toxic autonomously functioning thyroid nodule(s), and nontoxic multinodular goiter. The mechanism of I-131 results from the beta radiation (90%) producing radiation thyroiditis and chronic gland atrophy usually in 3-6 months but the symptoms are abated in 4-6 weeks. To solve for the dosage levels, these factors should be considered: Maximal amount of I-131 taken by gland, size and amount of tissue to be irradiated, effective half life of the isotope in the thyroid and relative sensitivity of the thyroid to I-131. Important considerations include that the diagnosis must be confirmed clinically and biochemically and nature of thyrotoxicosis must be determined. It is ideal to treat patients first with antithyroids (2 weeks at least) prior to therapy, discontinue antithyroids and no iodine rich foods at least five days prior to therapy. Dosing and choice of treatment must be individualized and pregnancy and lactation are absolute contraindication to radioactive ablation.

Comparison among the 3 regimens-relapse and recurrence is 60-70% with ATD’s and only 5-20% for RAI, hypothyroidism is 10-15 % after 15 years while with RAI 10-30% after first 2 yrs; with surgery it is independent on whether STT or NTT and cost is cheapest with RAI followed by ATD’s and surgery.

Advantages of I-131: It is safe- no complications other than hypothyroidism, no hospitalization, low cost, rapid elimination of goiter and symptoms, highly effective -higher dose increases success rate but higher chance of hypothyroidism. It follows a logarithmic pattern in terms of cure. Some studies have shown increase of hypothyroidism irrespective of dose. Studies have found no effect on fertility, no increased incidence of congenital malformations, and no increased risk of cancer in patients treated with radioactive iodine or in their off- spring. Finally, treatment should be individualized and tailored to each patient. Patients should be told of the various modalities of treatment, advantages and disadvantages of each giving them options. The need for continued follow-up through the years should be emphasized. Preference of treatment with various countries as the US, Europe and Japan will be discussed. Likewise dosing with various
methods will be included. Newer treatment options under investigation include endoscopic subtotal thyroidectomy, embolization of the thyroid arteries, plasmapheresis, and percutaneous ethanol injection of toxic thyroid nodules. Autotransplantation of cryopreserved thyroid tissue may become a treatment option for postoperative hypothyroidism. Nutritional supplementation with L-carnitine has been shown to have a beneficial effect on the symptoms of hyperthyroidism, and L-carnitine may help prevent bone demineralization caused by the disease.

O-018

Graves’ Ophthalmopathy

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Overt Graves’ ophthalmopathy (GO) develops in about 50% of patients with Graves’ disease. Even in patients without clinically apparent ophthalmopathy, orbital imaging reveals subtle infiltrative changes in an additional two-thirds of patients. Women develop GO more frequently than men. However, the eye changes tend to be more severe in men and in older patients.

The manifestations of GO are diverse. Characteristic signs and symptoms include retrobulbar ache, gritty sensation, redness of the eyelid and conjunctiva, eyelid retraction, exophthalmos and extraocular muscle dysfunction. Sight-threatening optic neuropathy is rare, reported in less than 5% of patients. In the majority of patients, the manifestations are mild, progressing through an initial active phase that subsequently burns out spontaneously without specific intervention.

The pathogenesis of GO is not completely understood. Both humoral and cellular mechanisms are believed to be involved, with the orbital fibroblast playing a key role in the inflammatory process leading to muscle volume and fat volume expansion. The TSH receptor has been identified as a shared antigen between the thyroid gland and orbital tissue, and is implicated in initiating and sustaining the autoimmune reaction.

Many studies have demonstrated an association between cigarette smoking and development of GO. Patients who smoke tend to have more severe eye signs and respond less well to treatment. Smoking is also associated with an increased risk of worsening eye signs following radioiodine therapy.

The management of GO is largely determined by the activity and severity of the disease in an individual patient; eg. patients with inactive disease respond poorly to immunosuppressive therapy, while rehabilitative surgery should not be carried out in the active phase. Mild clinical manifestations are usually adequately managed with local topical treatment such as lubricants, while sight-threatening GO requires immediate medical or surgical intervention. In patients with moderately severe, active GO, the benefits of treatment need to be balanced against the risks of side effects.

O-019

Thyromomics

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In several spheres of our life, there is monotony to many of our day to day activities, may it be personal, social or professional. We more often than not, continue to do the same thing in the same way for the same objective and if not same, for a similar end result or response. There are some in this world, who do not practice and believe in the boredom of repetitiveness and want every thought, every action and every reaction to be constructively different and challenging. Change has a considerable psychological impact on the human mind. To the fearful it is threatening because it means that things may get worse. To the hopeful it is encouraging because things may get better. To the confident it is inspiring because the challenge exists to make things better. Such fearless, optimistic and convinced individuals “Think Different” and “Do things Different” and more are less with their thoughts and deeds makes it possible that things works better. I consider myself very fortunate to be in this unique segment and contribute to India’s healthcare diagnostic industry. The last 16 years has been a dream journey for me.

I after my graduation in mathematics got an employment as a research scientist in one of the prestigious and world renowned leading Nuclear Research Institute in India. At this institute, I got an opportunity to learn, work and use a Nobel Prize winning technology “Radioimmunoassays (RIA)” and was extensively involved in doing laboratory in-vitro thyroid hormone investigations using RIA. My interest in thyroidology grew over the years and a research inquest on thyroxine binding globulin abnormalities gave me a Ph.D degree in Thyroid Pathophysiology. My professional expertise and the Doctorate ignited within me a thought for a change...to do things different from what it is at present. I wanted to explore laboratory business and felt that it is either now or never – to do this business. I had two options in mind:

1. To do what every other lab does – all tests under the sun without any focus.
2. To do only Thyroid and work on volumes – with a focus.
I decided to work on the second option and dreamt to have a company or a brand in India (Mumbai) that would operate as a single centralized laboratory and cater to a massive 1.2 billion population. The brand “Thyrocare” thus evolved and over the last 16 years, year over year it has exponentionally grown in business volumes, both in terms of specimens tested and turnover, and today it is valued at 200 Million USD in the healthcare market.

Several factors influence economics in laboratory testing and I take pride to term and refer the economics of my thyroid business as “Thyronomics”. The five most important pillars in the foundation and concept of Thyronomics were and are; Costs, Volumes, Quality, Speed and reach

Costs: In emerging economies, where for every laboratory test, patient still continues to pay dearly from his pocket costs indeed would matter a lot. In India, for every 10% reduction in costs, a 200% increase in volume can be observed. I chose RIA because it was less costly and reliable. However, to discourage me and put me out of business, my competitors labeled the RIA technology as “It is a less impressive technology” and “not a technology that holds truth”, which was indeed a lazy assumption. I continued with RIA and started my venture by daring to keep the cost of each test less than the cost of the reagents and generate enough specimen volumes. Competitors were shocked and stunned but I wanted to make my brand “totally” different from the rest. It took some time to get acceptance of my brand in the community and finally the Truth Triumphed.

Volumes: We realized that without the low cost, large volume is not possible and without large volumes, low cost also is not possible. The large volumes at our laboratory required large volume of reagents and the reagents because were purchased in large volumes came at a low cost. The reduction in reagent cost benefit was transferred to the patient’s investigation cost. On an average, we daily do 100,000 tests at our centralized laboratory and that makes our operation an unique and a rare one. Increased volumes necessitated us to go for automations, barcodes, bidirectional interfacing and that enhanced the quality of analytical testing and reporting. Also, it facilitated further reduction in the cost of entire load of specimen testing and to such an extent that today for a patient, Thyrocare as a brand, is the cheapest, nationally as well as globally. Our profitability using volumes has become attractive for many investors.

Quality: A large volume service requires stringent quality control and quality assurance programs. Cost of quality control programs remain constant and for those laboratories which focus and do great volumes, cost of keeping a vigilance and control on quality per sample or per test becomes as low as negligible. For an organization which does 3 million tests per annum, such programs cost just a two or three cents per sample. Quality also gets enhanced by quality manpower, quality procedures, quality operations and volumes help to teach, train and implement procedures that are essential to keep the errors as low as 1 in 10,000.

Speed: We have sample aggregators in all 530 district headquarters in the country, who keep visiting various hospitals and laboratories to collect the already collected specimen and later pack these in a purpose-built container before 5.00 pm, as per the guidelines of the brand. Using air-cargo logistics, all samples from various parts of the country are brought to Mumbai, every night, same night, before midnight. All analytical assay incubations take a minimum of 10 minutes to a maximum of two hours. For a laboratory that works only in night, it just takes maximum 4 hours to report on a given sample. If for some reasons, repeat testing is done, it takes additional 4 hours. For all the samples received, 90% are reported by 6.00 am, 99% reported by 8.00 am and 100% reported by 10.00 am. The innovation of IT has been maximally explored and utilized and its through IT enabled services we dispatch reports to 80% of Indian geographical locations with a turn-around-time (TAT) of 18hrs.

Reach: Only 2% of general population undergo laboratory thyroid investigations. If one is able to cover the entire length and breadth of the country, the volumes generated can run into several 1000s. By keeping a low margin, extending ourselves to the entire geography and working on volumes – has ensured fast growth of our network, a network constituted of dedicated and trained contracted manpower for sample collection. The entire billion population in India has an access to our services and we have nationalized Thyroid testing using our brand “Thyrocare” and that I have aptly christened as “Thyronomics”.

O-022

Radiosynovectomy in the Treatment of Arthritis

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Aim: Radiosynovectomy is a useful therapeutic option that involves radiopharmaceutical injections into joints, especially to treat rheumatoid arthritis. A problem for comparison of radiosynovectomy response is the lack of a gold standard for estimating the effect. Most papers used a subjective score by patients, which is uncertain. Therapeutic effects between 60 to 90% are described in the literature. Objective scoring, e.g. using the results of two-phase bone scintigraphy, is a good option in this topic. Liepe et al published data of bone scans before and after radiosynovectomy in 136 patients and 424 joints. The
Abstracts

Introduction: Chronic arthritis is a common clinical entity involving joints, bones, muscles, and tendons. Various treatment modalities are being used for the inflammatory arthritis ranging from non-steroidal anti-inflammatory drugs (NSAIDs), disease-modifying anti-rheumatic drugs (DMRDS), systemic corticosteroids, to intraarticular steroids and surgical synovectomy. However, these modes of treatment have certain limitations and high recurrence rate following discontinuation of therapy. Radiosynovectomy (RSV) is a local form of radiotherapy which is considered in inflammatory arthritis patients. A wide variety of radionuclide have been used for radiosynovectomy such as Y-90, Au-198, Er-169, Dy-165, Re-186 with an overall efficacy of more than 60%. Re-188 is a promising new radionuclide which has maximum β energy of 2.11 MeV similar to Y-90 making it very effective in larger joints. However, limited numbers of patients were recruited in these studies. Therefore, present prospective study was planned to see the efficacy of Re-188 in patients with chronic knee joints arthritis.

Aim: To evaluate the response of Re-188 tin colloid radiosynovectomy in terms of improvement of mobility, prolonged remission of disease, avoidance of surgery and reduction of analgesic use in patients with inflammatory knee joint conditions refractory to conventional treatment modalities.

Materials and Methods: Sixty-one knee joint in 48 patients with chronic synovitis due to various diseases who were refractory to conventional therapy (NSAIDS, DMRDS, Steroids and Immunosuppressant) were included in the study. Baseline blood pool bone scan was performed in all patients. In addition, clinical evaluation of mobility score (0 to 3), pain score (0 to 10), analgesic score (0 to 6), tenderness score (0-3) and joint swelling score (0-3) was also done. Radisynovectomy of knee joint was done using intra articular injection of 370-666 MBq of Re-188 tin colloid. Response of radiosynovectomy was assessed using various clinical scores mentioned above and blood pool bone scan, at 3, 6, and 12 months.

Results: Baseline bone scan showed mild, moderate, and severe increased blood pool in 4, 36 and 21 knee joints, respectively. At 3-months post radiosynovectomy follow up (52 joints) bone scan showed normal blood pool, mild and moderate increased blood pool in 46, 4, and 2 joints, respectively. 6-months follow up bone scan (54 joints) showed normal, mild, and moderate increased blood pool in 45, 7, and 2 joints, respectively. 12 months follow up (61 joints) blood pool showed normal, mild, moderate, and intense activity in 44, 6, 9, and 2 joints, respectively. None of the joints showed intense blood pool activity at 3 and 6 months. Baseline mean pain score was 6.8 ± 1.7 which reduced to 1.34 ± 1.78, 1.0 ± 1.7, and 1.36 ± 2.0 at 3, 6, and 12 months, respectively (P = 0.001). Baseline mean analgesic score was 6.8 ± 1.7 which reduced to 1.34 ± 1.78, 1.0 ± 1.7, and 1.36 ± 2.0 at 3, 6, and 12 months respectively (P = 0.001). Baseline mean tenderness score was 1.0 ± 0.7 which reduced to 0.7 ± 0.3,
0.08 ± 0.2 and 0.1 ± 0.3 at 3, 6, and 12 months, respectively \( (P = 0.001) \). Baseline mean joint swelling score was 1.6 ± 0.7 which reduced to 0.14 ± 0.54, 0.17 ± 0.42, and 0.25 ± 0.5 at 3, 6, and 12 months respectively \( (P = 0.001) \). Baseline mobility score was 1.46 ± 0.76, which reduced to 0.36 ± 0.60, 0.28 ± 0.58, and 0.41 ± 0.73 at 3, 6, and 12 months respectively \( (P = 0.001) \).

**Conclusion:** Re-188 tin colloid synovectomy is found to be a useful treatment modality in patients with inflammatory knee joint conditions refractory to conventional treatment modalities. Re-188 appears to be an ideal radionuclide for radiosynovectomy of larger joints like knee joint and superior to most of the existing radionuclides because of its better penetration of β-energy. In addition, Re-188 emits gamma energy of 155 KeV, which makes imaging possible for bio-distribution of radiotracer. It is available from Tungsten (W)-188/Re-188 generator, which makes its storage, transportation, elution and usage very convenient and cost-effective. This treatment modality has few minor side effects.

**O-023A**

**Radiosynoviothrosis (Radiation Synovectomy): State of the Art 2011**

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Radiosynoviorthesis (RSO) is a proven important instrument for local treatment of chronic inflammatory joint diseases in the context of medical and orthopaedic efforts. The term radiosynoviorthesis was created by Delbarre et al. 1968, meaning the restoration (orthesis) of the synovium by means of radionuclides. By local application of radioactive agents an attempt is made to influence the painful destructive synovial process favourably as an alternative to surgical synovectomy. In the anglo-american literature the term radiosynovectomy or radiation synovectomy came into use.

In Germany RSO nowadays is performed in about 63.000 joints per year, as much as radiiodine therapy in thyroid diseases.

Basically RSO is indicated for the local treatment of almost all kinds of chronic synovitis. The main indications for RSO are:

- Rheumatoid arthritis
- Seronegative spondarthropathy (i.e. reactive arthritis, psoriatic arthritis)
- Hemarthrosis in hemophiliac
- Recurrent joint effusions (i.e. after arthroscopy)
- Pigmented villonodular synovitis (PVNS)
- Osteoarthritis (Activated arthrosis)
- After joint prosthesis: persistent effusions, polyethylene disease
- Undifferentiated arthritis (where the arthritis is characterized by synovitis, synovial thickening or effusion)

The most common and approved radiopharmaceuticals used for RSO are following β-emitters:

- \([^{99m}\text{Tc}]\) yttrium-citrate or -silicate (\([^{99m}\text{Tc}]\) colloid), only used for RSO of knee joints
- \([^{186}\text{Re}]\) rhenium sulphide (\([^{186}\text{Re}]\) colloid), used for RSO of middle sized joints
- \([^{169}\text{Er}]\) erbium citrate (\([^{169}\text{Er}]\) colloid), used for RSO of small joints.

The radioactive particles in colloidal form are taken up by phagocytosis in synovial macrophages with homogenous distribution on the surface of synovium. β-radiation leads to coagulation necrosis, sclerosis and fibrosis of the synovial tissue including vessels and pain receptors, resulting in reducing effusion, swelling and pain of the joint. Cartilage has no nerves and vessels and cannot inflict pain and because of having no ability for phagocytosis this tissue is no target for the radiation effects.

Patients should be submitted after ineffective conservative local and/or systemic (rheumatic diseases) treatment. Also after surgical interventions RSO might improve the complaints of the patient, i.e. after total knee replacement or effusions after arthroscopy.

Side effects are very rare, and good efficacy of RSO is about 70-80 % for years by only one treatment. In some more difficult cases fractionated RSO may lead to success.

Diagnostic studies prior to RSO:

- Ultrasound study (obligatory prior to RSO to rule out a Baker’s cyst)
- Multiphase scintigraphy with \([^{99m}\text{Tc}]\)-MDP is the best diagnostic tool for detecting synovitis (soft tissue scintigraphy) and bone involvement (bone scintigraphy).

Performance of RSO requires a suitable room and strict asepsis. A good puncture technique is essential. Apart from the knee all joints have to be punctured for RSO by fluoroscopy and often by arthrography.

After RSO distribution scintigram confirms the appropriate intra-articular distribution of the radiopharmaceutical. Only after use of Erbium-169 no scintigram is available.

Immobilization of the treated joints by a splint is required for 48 hours avoiding necrosis and leakage.

The first follow-up care is recommended about 6 months after RSO or earlier, of course, when problems (reactive inflammation, suspect of infection, swelling of Baker’s cyst) occur.

**Results:** Response rates reported in abundant literature range from about 60 to >80% for all joints, often with greater success for rheumatoid diseases.
than for osteoarthritis. Most of the studies relating to RSO during the last 40 years do not fulfil the criteria of modern evidence based medicine, but recently a number of well designed trials have been carried out evaluating the efficacy of RSO. RSO provides better results in rheumatoid arthritis than in osteoarthritis, depending on stage of joint damage. Deformed or unstable joints might fail treatment and therefore surgical interventions should be considered. Close cooperation with orthopaedists and rheumatologists is necessary to consider RSO in each patient to ensure optimal medical care. Education in all fields of RSO is possible in our German Centre for Radiosynoviotherapy.

O-024

New DOTA-based Bisphosphonate Ligands for PET/CT and Endoradiotherapy of Bone Metastases

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Aim: Bone metastases are often a severe appearance in patients suffering from cancer. An early diagnosis and localization is beneficial for therapy. 99mTc-derivatives of bisphosphonates are already used for imaging of osteoblastic metastases with SPECT/CT. It was possible to synthesize three new macrocyclic bisphosphonates. Using the 68Ge/68Ga-generator system, these DOTA-derivatives are available for PET diagnosis of bone metastases. In terms of THERANOSTICS it is also possible to label these compounds with 177Lu for treatment.

Materials and Methods: The three DOTA-based bisphosphonates BPAMD, BPAPD and BPPED were labeled with 68Ga and 177Lu, followed by animal PET studies with healthy and bone tumor-bearing rats. Standard-uptake-values (SUV) have been obtained for the 68Ga-derivatives. A first human diagnostic study was realized with [68Ga] BPAMD and compared to [18F] Fluoride in first human studies. [68Ga] BPPED showed significant higher bone uptake values in animals and is under further investigation. By using 177Lu instead of 68Ga, endoradiotherapy is possible with the same compound and [177Lu] BPAMD showed promising results in human studies. The advantage of these complexing compounds is the possibility of bridging quantitative pre-therapeutic diagnosis and dosimetry with generator-based 68Ga and subsequent therapy with 177Lu using the same precursor, representing the excellent applicability for THERANOSTICS.

O-029

“Theragnostic” Radiopharmaceuticals: An Emerging Paradigm Empowering Personalised Medicine

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During the past three decades, the area of the production and applications of therapeutic radionuclides and radiopharmaceuticals has undergone through the rapid and constant evolutionary cycles of nuclear medicine - starting with empirically prepared radiopharmaceuticals in the past to the present intelligent designing of specific agents for molecular imaging and targeted therapy. Unfortunately, among all the radionuclides that have
ever been produced, or those that continue to be investigated for production, only a very few have or will end up with the required combination of favorable nuclear, physical, and biological characteristics to become clinically useful imaging or therapeutic medical radionuclides.

Rapid advances in molecular biology continue to lead to a better understanding of cancer and other disease states, and parallel research has shown promise for biological vehicles such as monoclonal antibodies, specific proteins and peptides, and a variety of other systematically designed (“tailor-made”) molecules, to serve as specific carriers to deliver imaging photons to diagnose disease, or therapeutic electrons to deliver cell killing radiation, in a highly localized fashion. These developments have led to a renewed interest in the exciting possibility of treating, in particular, the disseminated human malignancies and various other disorders with the systemic administration of radionuclides. A number of relatively new radiotherapeutic modalities and procedures, such as the treatment of metastatic bone pain, radiation synovectomy, bone marrow ablation, and treatment of inflammatory diseases including cancer and cardiovascular lesions, etc., have given additional impetus to need for research on therapeutic radionuclides matched with the requirements of specific applications.

A major advantage of radionuclides is that they emit radiation of different radiobiological effectiveness and range of action. This offers the possibility of choosing a nuclide the physical and nuclear characteristics of which are matched with a particular tumor type, or the disease under treatment. In this presentation, we will introduce a relatively novel paradigm that involves specific individual radionuclides or radionuclide pairs that have emissions that allow pre-therapy low-dose imaging plus higher-dose therapy in the same patient. We have made an attempt to sort out and organize a number of such dual-purpose theragnostic radionuclides and radionuclide pairs that offer this exciting potential of low-dose imaging followed by higher-dose treatment and thus possibly bringing us a major step closer to personalized medicine.[1, 2] This approach would empower the age-long dream of performing individualized or tailored radionuclide therapy in cancer patients, as well as in the treatment of many other disorders that respond to radionuclide therapy. However, an increased and reliable availability of theragnostic radionuclides remains a major issue, which will also be addressed. It should be stressed that ideally, it would be best to use the same theragnostic radionuclide, or its close congeners with the same electronic structure, and therefore with the same chemical and biochemical properties, so that imaging predicts biodistribution and dosimetry in a reliable, individualized fashion, and thus also predicts as to which patients will respond to the radionuclide therapy procedure being considered and which will not. In the second best situation, a radionuclide pair (imaging photon emitter, either gamma or positron, and therapeutic particle emitter, with the same electronic structure) can be used as well. One caveat here that is a fact of life is, that even though such isotope pairs may have the same electronic structure, their specific activities and the production and processing methodologies may be different and thus their chemistry as well, due to the different chemical nature (species, charge, etc.) and/or the quantity of radioimpurities and chemical contaminants, which cannot be totally removed.

A low-dose administration using radiopharmaceuticals based on these theragnostic radionuclides or radionuclide pairs would initially allow molecular imaging (SPECT/CT or PET/CT) to provide the necessary pre-therapy information on biodistribution, dosimetry, the limiting or critical organ or tissue, and the maximum tolerated dose (MTD), etc. If the imaging results then warrant it, it would be safe and appropriate to follow up with dose ranging experiments to allow higher-dose targeted molecular therapy with the greatest effectiveness. This is especially important in order to be able to do tailored imaging plus therapy (personalized medicine) in individual patients.

This presentation will discuss a number of individual radionuclides and radionuclide pairs that emit both imaging photons and therapeutic electrons and which would be potentially excellent choices for theragnostic applications. Since the overall story (including preliminary clinical trials) is a bit more complete in the case of tin-117m,[3] a conversion electron emitter with great theragnostic potential, it will be discussed in more detail, as an example. At BNL, our work on radionuclide therapy has for some time focused on the development of this radionuclide for application to several distinct clinical areas. These include palliation of bone pain from osseous metastases, treatment of metastatic bone disease, radiation synovectomy, radioimmunotherapy, and cardiovascular applications.

Tin-117m ($T_{1/2}$ 14.0 d; $γ$ 159 keV, 86%) is a very promising radionuclide for the development of theragnostic radiopharmaceuticals. In contrast to most other therapeutic beta emitters, Sn-117m decays via isomeric transition with the emission of monoenergetic conversion electrons (127, 129, and 152 keV; abundance 65, 12, and 26% respectively). These emissions have short discrete ranges of between 0.22 and 0.29 mm in water. Therefore Sn-117m is effective for therapy of metastatic disease and for certain other inflammatory conditions (e.g., atherosclerotic disease) causing much reduced myelosuppression and greatly reduced dose to normal organs. Moreover, having the 159 keV $γ$-photon, $^{117m}$Sn is
perfect for pre-therapy imaging in the same patient. The results of the Phase II clinical trial of tin-117m DTPA for bone pain palliation (using reactor-produced tin-117m, with specific activity ranging between 8-20 Ci/g of tin) will be presented.

In more recent work, Sn-117m-electroplated stents were implanted in aortas of hyperlipidemic rabbits and in pigs with damaged coronary arteries, and it was demonstrated that Sn-117m could reduce inflammatory events following stent implantation. When delivered systematically to atherosclerotic tissue using specific targeting molecules (e.g., Annexin), Sn-117m could also provide a means in low doses to image and in higher doses to reduce the vulnerability of the active atheromatous disease (vulnerable, or unstable plaques) in the coronary arteries. These studies are in progress and a Phase I/II clinical trial initiated in early 2010 is in progress. NCA tin-117m is also being developed and tested for the therapy of bone metastases and for use in radioimmunotherapy.

In short, this paradigm when properly enforced would constitute a major step forward to meet the challenges of enabling personalized medicine. Theragnostic radiopharmaceuticals have the power to drive advances in personalized medicine that will offer better-targeted diagnosis and treatments. Using this approach, it would be possible to envision a future where treatments are tailored to individuals' specific disease parameters and where imaging data could be analyzed in real-time and in advance to predict likely effectiveness of therapy and learn what would or would not work. Implementation of this regimen potentially creates a situation where treatments are better targeted, health systems save money by identifying therapies not likely to be effective for particular people, and researchers have a better understanding of comparative effectiveness.

To reemphasize, this modality would empower us to carry out molecular imaging plus molecularly targeted therapy in the same patient using the same radiopharmaceutical and thus would be an exciting development with a very promising future, and possibly of invaluable benefit to cancer patients.

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O-030

**The Oncidium Foundation: A Perspective**

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Nuclear physicians working in the field of therapy know how difficult it is to convince the community to put more efforts in the development of new radiolabelled therapeutic molecules. WARMTH is at the forefront in increasing awareness about this modality. Despite the successes that have been recorded with radiotherapeutic in last chance cancer treatment and the network of therapeutic sites and expert groups that has been established, the scientists and physicians are still lacking the necessary financial support for the development of this efficient therapeutic modality. Numerous molecules that have demonstrated their potential utility are on hold as the funds required to perform the most expensive phase III clinical trials are awaited. As time goes by, the patent rights for these radiotherapeutics are being lost one by one, hence diminishing further interest from investors and reducing further the chances that they will one day appear on the market. Reasons for this lack of interest in radiopharmaceuticals became with time quite obvious for the nuclear medicine community.

The pharmaceutical world stakeholders give a different priority to this technology as a consequence of its supposed complexity, the apparent limited market size and the lack of a big success story. In the absence of convinced potential investors, philanthropic donations can offer a prime means of boosting this technology. The Oncidium Foundation was created to achieve this (expensive) goal by promoting radiotherapeutic and financing the marketing of already well-developed drugs which could benefit hundreds of thousands of cancer patients. A desirable level of success would be to bring at least three to five of these drugs onto the market, with the first appearing within three years following the creation of the Foundation. Oncidium is already supported by WARMTH, EANM, SNM, AIPES, as well as the companies IBA, IRE and CEN-SCK. The aim, the concept and financials will be explained. The status of development of the Foundation at the time of the talk will be presented and physicians already involved in the use of this technology will be informed how they can at their individual level participate. Details about the Oncidium Foundation, its aim, its needs, its initial structure, can already be found on the web under www.oncidium-life.org where a full descriptive document can be uploaded for the largest as possible distribution.
Regulatory Aspects of Therapeutic Radiopharmaceuticals

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Radiopharmaceuticals are medicinal products and classified as prescription-only medicine. Clinical use of therapeutic radiopharmaceutical is governed by the Medicines Act in many countries. Currently, therapeutic radiopharmaceuticals are used in the following ways; (1) registered products (marketing authorisation or product license) by one of the reference regulatory agencies and approved by the national drug regulatory authority, (2) magistral preparation of radiopharmaceuticals in accordance with the pharmacopoeia method, (3) in-house preparation of radiopharmaceuticals under the supervision of nuclear medicine physician for his own patients with or without GMP or cGRPP conditions, and with or without ethic committee or IRB approval, (4) clinical trial certificate or special permit issued by the relevant regulatory authority for investigational new drug, or (5) none of the above. Due to increasing complexity of the regulatory mechanisms and safety concerns, condition 5 may not be an option for the use of therapeutic radiopharmaceuticals. For descriptive purpose for regulatory consideration, therapeutic radiopharmaceuticals can be classified into three groups.

The first group of therapeutic radiopharmaceuticals are commercially available as ready-made compounds which can be used directly as unit doses. These therapeutic radiopharmaceuticals are registered and can be imported and used by the jurisdiction of nuclear medicine physicians.

Second group of therapeutic radiopharmaceuticals are those which can be prepared as magistral preparation in accordance with pharmacopoeia. European Pharmacopoeia mentions monographs on Iobenguane (\textsuperscript{131}I) for therapeutic use, Sodium iodide (\textsuperscript{131}I) capsules for therapeutic use, Sodium phosphate (\textsuperscript{32}P) injection, and Strontium (\textsuperscript{89}Sr) chloride injection. United States Pharmacopoeia mentions Iobenguane (\textsuperscript{131}I) Injection, Sodium Iodide (\textsuperscript{131}I) Capsules, Sodium Iodide (\textsuperscript{131}I) Solution, Samarium (\textsuperscript{153}Sm) Lexidronam Injection, Strontium Chloride (\textsuperscript{89}Sr) Injection, and Yttrium (\textsuperscript{90}Y) Ibritumomab Tiuxetan Injection. Since all of the products mentioned in the pharmacopoeia are available commercially, magistral application may not be applicable for this group.

Third group of therapeutic radiopharmaceuticals are those without product license or not yet mentioned in the pharmacopoeia. Majority of targeted therapeutic radiopharmaceuticals belong to this group. Some therapeutic radioisotopes, such as \textsuperscript{188}Re, are available as generator. Neither generator nor radioisotope nor chemicals (ligands) are registered in any of the reference drug regulatory agencies. That has led to the fact that these therapeutic radiopharmaceuticals have to be prepared in-house in the nuclear medicine radiopharmacy under the supervision of nuclear medicine physician and radiopharmacist as qualified person for production.

All drugs including radiopharmaceuticals must be fit for its intended use, which means product quality attributes such as safety, potency, and efficacy must be met. Radiopharmaceuticals’ physical, chemical, biological, or microbiological property or characteristic should be within an appropriate limit, range, or distribution to ensure the desire quality. In order to meet the critical product quality attributes, preparation of radiopharmaceuticals for routine clinical use needs to follow guidelines on current good radiopharmacy practice (cGRPP) such as Part B of cGRPP recommended by the European Association of Nuclear Medicine (EANM): Guidelines on cGRPP for locally prepared radiopharmaceuticals. Routine preparation of radiopharmaceuticals requires implementing a quality plan consisted of quality assurance program and quality control measures. It is important to note that quality cannot be tested into products; it has to be built in by design (Quality by design – QbD). Adoption of quality management system, good documentation practice and cGRPP could satisfy future application of regulatory permits, certificates and licenses to an extent.

Due to the high sensitivity and selectivity of nuclear medicine procedures, molar probe-mass required for radiopharmaceutical is very low, 1 to 100 ng, and usually cannot provoke any pharmacological response. However, application of radiopharmaceuticals in patients requires thorough consideration and calculation of radiation dose to ensure that potential benefits outweigh risks and damages caused by radiation. It is important for diagnostic applications and more important for therapeutic radiopharmaceuticals. Information on pharmacokinetics should be sufficient for radiation dosimetry calculations. Calculations of absorbed dose to organs should be carried out in accordance with the Medical Internal Radiation Dosimetry (MIRD) schedules. In addition to the requirement for acute radiation dose consideration, FDA has released draft guidance on “Non-clinical Evaluation of Late Radiation Toxicity of Therapeutic Radiopharmaceutical” to provide recommendations for designing nonclinical late radiation toxicity studies to determine potential late radiation effects of therapeutic radiopharmaceutical agents.
O-032

Clinical Applications of SPECT-CT in Oncology

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Nuclear medicine performs functional measurement by injecting the patient with target radiopharmaceuticals that are accumulated in response to its biochemical or metabolic characteristics. Imaging methods such as X-ray computed tomography (CT) and magnetic resonance imaging (MRI) could be used to evaluate morphological structural abnormalities with high spatial resolution. SPECT-CT technique produces anatomical and functional imaging with the patient in the same position. During a single procedure image co-registration and fusion process are obtained. CT information is used for attenuation correction of SPECT study to perform high-quality images. Both sensitivity (correct anatomical topography of abnormal uptake) and specificity (reduction of false-positive results due to physiological tracer bio-distribution) of fusion images are increased. Diagnosis, staging and monitoring visual procedures are gaining a major role in the management of cancer patients. This presentation has submitted several useful clinical applications of SPECT-CT in oncological practice. SPECT-CT studies have a limited role for the diagnosis and staging of malignant diseases mainly for the pre-treatment imaging and localization of neuroendocrine tumors using 111In-OctreoScan or 131I-MIBG; for visualizing of primary breast cancer and/or regional lymph nodes using 99mTc-Sestamibi or 99mTc-Tetrofosmin etc. Mapping of sentinel lymph nodes on fusion images is widely applicable in breast, head and neck, cervical cancers, melanoma etc. The most important role of SPECT-CT is to evaluate treatment response in oncology with different target radiopharmaceuticals for corresponding malignancies. Main clinical applications after final therapy are as follows:

- Differential diagnosis of residual tumor tissue from fibrosis and necrosis.
- For early determination of relapse in cases with abnormal clinical and laboratory indices.
- For precise topography of metastatic foci in patients with disease extension.
- For differential diagnosis of malignant from benign lesions and physiological uptake.

For assessment of therapeutic response of metastatic disease: full, partial, stable or progressive SPECT-CT studies are also used for planning in radiotherapy to target precise tumor volume delineation. In conclusion by using functional SPECT modalities to complete anatomical CT imaging, clinicians can obtain more information to plan their surgical and/or therapeutic management of cancer patients.

O-033

Radiopharmaceutical and Molecular Therapy Quiz

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Abstract not available.

O-034

Targeted Chemoradiation in Metastatic Colorectal Cancer: A Phase I trial of $^{131}$I-huA33 with Concurrent Capecitabine

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Purpose: HuA33 is a humanized antibody that targets the A33 antigen, which is highly expressed in intestinal epithelium and >95% of human colon cancers, but not other normal tissues. This phase 1 study used radiolabelled huA33 in combination with capecitabine to target chemoradiation to metastatic colorectal cancer. The primary objective was safety and tolerability of the combination of capecitabine and $^{131}$I-huA33. Pharmacokinetics, biodistribution, immunogenicity, and tumor response were also assessed.

Materials and Methods: Eligibility included measurable metastatic colorectal cancer, adequate hematological and biochemical function, and informed consent. An outpatient scout $^{131}$I-huA33 dose was followed by a single therapy infusion one week later, when capecitabine was commenced. Dose escalation occurred over 5 dose levels. Patients were evaluated weekly, with tumor response assessment at the end of the 12 week trial.

Results: Nineteen patients were enrolled (13M: 6F, age range 49-67 yrs), and 18 pts were evaluable.
The most frequently observed toxicity included myelosuppression, gastrointestinal symptoms, and asymptomatic hyperbilirubinaemia. Biodistribution analysis demonstrated excellent tumor targeting of the known tumor sites, expected transient bowel uptake, but no other normal tissue uptake. $^{131}$I-huA33 demonstrated a mean terminal half-life and serum clearance of $T_{1/2}^{\beta}=100.2 \pm 20.9$ hrs; $CL = 36.7 \pm 8.0$ mL/hr. One patient had a partial response, and 10 had stable disease, and prolonged progression free survival (4 - 48 months) was observed.

**Conclusions:** $^{131}$I-huA33 achieves specific targeting of radiotherapy to sites of metastasis and can be safely combined with capecitabine. This provides an opportunity to deliver chemoradiation specifically to metastatic disease in colorectal cancer patients.

**O-035**

**Targeted Radionuclide Therapy of Liver Tumors**

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Abstract not available.

**O-036**

**Clinical Efficacy of Radioembolisation using $^{188}$Re-Human Serum Albumin Spheres in Patients with Progressive, Unresectable Primary or Secondary Liver Cancers: A comparison to Standard Approach Using $^{90}$Y Sir-Spheres**

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**Introduction:** Radioembolisation using radioactive spheres in patients with advanced, unresectable liver primary or secondary cancers is currently used as effective palliative therapy in those patients who has no other option of further effective therapy. Most papers about Selective Internal Radiation Treatment (SIRT), concentrate on use yttrium ($^{90}$Y) radioisotope coated on resin or glass spheres. This type of treatment is effective even large tumor mass within liver due to directly hepatic arterial administration of radioisotope into cancer feedings artery. Permanent deposits of radioactive spheres into tumor vascular bed, cause elimination of cancer cells using high energetic b-electrons, that have lower toxicity to the normal tissue, due to direct deposition within tumor. However using $^{90}$Y spheres there is some drawbacks, like high price of commercially available products (Sit-Spheres and Terra-Spheres), dependency of possible overseas shipment, which could be affected by many factors. Also $^{90}$Y as a pure beta emitter give us only Bremstrahlung post-therapy images, which could be not optimal to precise evaluation of radioactive deposition within tumor lesions. $^{188}$Re seems to be very attractive radioisotope, in this type of therapy, which could be used anytime in standard nuclear medicine department within the working days, due to generator production and self labeling, using kits of HAS spheres. Another advantage of $^{188}$Re human serum albumin (HSA) microspheres is a high stability of the radiopharmaceuticals seen in vitro and in vivo studies as well.

**Background:** To evaluate the clinical and radiological effectiveness of radioembolisation (RE) using $^{188}$Re-human serum albumin (HSA) microspheres in patients with advanced, progressive, unresectable primary or secondary liver cancers, not suitable to any other form of therapy with long term follow-up. The second goal of this study was to compare RE using $^{188}$Re HSA to standard approach using $^{90}$Y Sir-Spheres in terms of PFS (progression free survival) and OS (overall survival).

**Materials and Methods:** Overall 13 patients (pts) with 20 therapy sessions had RE with $^{188}$Re HSA microspheres. Second group of 15 pts with 23 therapy sessions had RE using $^{90}$Y Sir-Spheres. The administered activity of $^{188}$Re HSA was calculated base on empirical methods, depended on tumor/liver involvement and functional status of the liver and general patient condition. The administered activity of $^{90}$Y Sir-Spheres was base on commercial recommendation. Sequential post-therapy scans were used to calculate personal internal dosimetry in case of. Clinical responses were assessed, 6 weeks (W) after completing therapy, and then after each of the 3 months (M). The objective radiological response was classified according to RECIST v. 1.1 by sequential MRI. Toxicity was evaluated using CTC NCI v. 3.1.
Results: There were 4 HCC pts, rest of them with metastatic cancer. RE performed in catheterization of the left or right hepatic artery, if both lobes involved separate session was performed. Mean administered activity of $^{188}$Re HSA was 7.24 GBq (3.8-12.4). Median OS in all pts was 6 M and PFS 4M, there was no difference between OS nor PFS in pts with primary or metastatic disease. In selected group of patients those who had clinical partial response(PR), or stable disease (SD), and disease progression (DP) 6 weeks after therapy median OS was 9/5/4 M and PFS 5/2/0 M. Very high labeling efficacy over 97+2.1% and very low urinary excretion of $^{188}$Re was noted 6.5±2.3%. The toxicity was an acceptable level, immediately after therapy only grade 2, after 6 W of therapy single case had grade 3 (bilirubin and liver enzymes). After 3 M grade 3 toxicity was noted in 4 pts (bilirubin), 2 pts (liver enzymes) and single albumin depletion, mostly related to rapid cancer progression. After 3 M radiological response was reported only in 2 pts, stable disease in 13 pts and rest had disease progression.

Conclusion: RE using $^{188}$Re HSA seems to be an option of palliative therapy in patients with extensive progressive liver involvement cancer. Is well tolerated in most of the patients with low level of toxicity during and within 3 months of follow-up.

O-037

PET/CT is Better than CECT in the Assessment of Response to $^{90}$Y-Microspheres in the Treatment of Liver Tumors

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Primary Liver Tumors are common malignancies with unsatisfactory treatment and bad prognosis with HCC among the 10 most common cancers. Aetiology related to the incidence of hepatitis B virus with highest incidence in SE Asia and Africa. Secondary Liver Tumors are most common tumors of the liver, commonly from GI tract via the portal venous system but other metastases from lung, prostate, breast, pancreas, stomach, kidney, cervix, and ovary.

Treatment options: Surgical resection is the treatment of choice if functional reserve is adequate but only 5-10% are candidates for potentially curative resection due to advanced disease. Post resection 5-year survival in HCC is ~50%. External Beam Radiation Therapy has a limited role in the treatment of liver tumors due to damage to normal liver parenchyma and to surrounding organs. Systemic Chemotherapy is generally ineffective in HCC with short duration response rate of < 20%. Similar results in liver metastasis with survivals of ~ 12 months and partial response of 20% to 30%. Other methods like RFA, Cryo and Laser therapy have their own limitation. $^{90}$Y-Microspheres Provides a method of selectively irradiating tumor cells due to preferential blood flow via hepatic arteries to malignant deposits, which supply 80-90% of tumor blood flow. The portal vein supplies mostly the healthy liver tissue. The contraindications include: History of external beam radiotherapy, Ascites or clinical liver failure, Hepatopulmonary shunt > 20%, Pre-assessment angiogram demonstrating significant reflux of hepatic arterial blood to the stomach, pancreas or bowel and Disseminated extra-hepatic disease Methodology.

Diagnostic angiography: Assess the visceral arterial anatomy and identify vessels that may cause reflux and vascular embolisation performed to prevent microspheres reaching non-target organs.

Assessment of hepatopulmonary shunt: This is used during angiography by injecting $^{99m}$Tc-MAA in the hepatic arteries and quantitating degree of shunt to lungs

Dose calculation: Depends on several factors: Tolerance of the liver to ionizing radiation, The magnitude of liver involvement: Greater bulk = more blood flow= more effect and Degree of hepatopulmonary shunt: More shunt = smaller dose.

Complications: Abdominal pain, fever and nausea; Pain that does not remit may suggest pancreatitis cholecystitis, peptic ulceration; Radiation Pneumonitis, Radiation Hepatitis.

Our experience: Between June 2004 and December 2011 we have treated 130 patients with liver tumor. Age range 35-78 years. Most patients were hepatic metastases from colorectal carcinoma (60%) followed by Cholangiocarcinoma (13%) and others. There were only 3 patients with HCC (3.5%). 6 patients received 2 treatments, Treatment was well tolerated. Improved quality of Life and Survival. Nine Patients had complications all resolved with appropriate measures Follow up with PET is better than CT.

Response on PET/CT was highly correlated with LDH ($P<0.0001$), CEA ($P=0.01$) and Ca19-9 ($P=0.02$) while there was no correlation with CECT criteria. PET/CT predicted PFS and separated PR (12 months median PFS) from SD (5 months median PFS) with $P<0.0001$. No correlation using CECT criteria.

Conclusion: 90Y-Microspheres is a good treatment for unresectable extensive liver tumors but needs careful patient selection that involves various specialities. Has been shown to improve QOL and reduce tumor size and metabolic activity. Assessment of response with PET/
CT was correlated well with PFS and tumor markers unlike CT alone.

O-038

Molecular Radiotherapy in the UK: The Current Status

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Whilst the use of radionuclide therapy has been available for 60 years there is still great variation in both the availability of these treatments and the type of centres offering these treatments. The British Institute of Radiology (BIR) is Britain’s premier organisation for the study of the use of ionising radiation in humans and includes both clinicians and scientists. In 2008, the BIR commissioned a survey of the use of radionuclide therapy, which they titled molecular radiotherapy throughout the 4 nations of the United Kingdom. A total of 200 hospital organisations were contacted and replies obtained by over 80. Unsurprisingly the most common form of treatment offered was I-131 for benign and malignant thyroid disease. The second most common form of treatment was I-131 MIBG with two centres specialising in treatment of neuroblastoma in children. A handful of sites offered other molecular radiotherapy treatments. Overall, it was found that most treatments were offered in London or North West London; outside of these areas provision was patchy. Those centres lead by nuclear medicine physicians offered the widest range of treatments and had the higher level of physics input. Though available, the ability to access molecular radiotherapy depends mostly on where you live in the UK.

O-039

Odds Ratio, Relative Risk, and Hazard Ratio

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Odds ratio (OR) is a statistic commonly encountered in professional or scientific medical literature. Most readers perceive it as relative risk (RR), although most of them do not know why that would be true. But since such perception is mostly correct, there is nothing (or almost nothing) wrong with that. It is nevertheless useful to be reminded now and then what is the relation between the relative risk and the odds ratio, and when by equating the two statistics we are sometimes forcing OR to be something it is not. Another statistic, which is often also perceived as a relative risk, is the hazard ratio (HR). We encounter it, for example, when we t the Cox model to survival data. Under proportional hazards it is probably "natural" to think in the following way: if the probability of death in one group is at every time point k-times as high as the probability of death in another group, then the relative risk must be k, regardless of where in time we are. This could be hardly further from the truth and in this talk I will try to dispense with this blunder.

O-041

Peptide Receptor Radionuclide Therapy - The Innsbruck Experience

Irene Virgolini and NET-Team (Daniel Putzer, Dietmar Waitz, Bernhard Nilica, Alexander Kroiss, Sabine Buxbaum, Vlado Stefanovic, Dorota Kendler, Christian Uprimny, Clemens Decristoforo, Elisabeth von Guggenberg, Roland Haubner, Boris Warwitz, Martin Jeller, Eva Gamper, Remigius Orjiukwu, Michael Gabriel, Roy Moncayo)

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We are going to report our experience with Peptide Receptor Radionuclide Therapy (PRRT) since IV/2005 when our new therapy ward was installed according to the principle of "architecture and healing". We shall introduce our interdisciplinary team work. We shall overview our clinical outcome results in the light of patient care. We conclude that PRRT is an 1. effective treatment option for >75% of patients (complete remission, partial or minor response, stable disease), 2. has a long progression-free survival and 3. has a low rate of side effects (renal, bone marrow). Response predictors are the 1. extent of tumor disease (liver, bone involvement) 2. Functional imaging: $^{68}$Ga-somatostatin receptor PET +/- $^{18}$F-FDG-PET 3. Karnofsky score. An improved Quality-of-Life is seen in 2/3 of patients following PRRT.
O-042

Peptide Receptor Radionuclide Therapy of Neuroendocrine Tumors - The Bad Berka Experience after 10 Years in Over 1000 Patients

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Introduction: Neuroendocrine tumors (NETs) are relatively rare tumors originating from neuroendocrine cells, distributed ubiquitously throughout the body. The term “neuroendocrine” relates to a peculiar characteristic or phenotype of these cells, namely the ability of synthesize, store and secrete neurotransmitters or neuromodulators, substances produced by both the endocrine and nervous systems. The most common sites are lung/bronchus, ileum and rectum. The gastroenteropancreatic neuroendocrine tumors (GEP-NET) constitute 75% of all NETs. The current WHO classification distinguishes 3 groups of GEP-NET; reflecting roughly the different biology of tumors – highly differentiated neuroendocrine tumor with a proliferation rate (Ki-67) of less than 2%; highly differentiated neuroendocrine carcinoma with Ki-67 greater than 2% and low differentiated neuroendocrine carcinoma with Ki-67 greater than 20%. Vascular and lymphatic invasion and metastases are the criteria for malignancy. The heterogeneous nature of neuroendocrine tumors, their indolent course and the lack of optimal conventional therapy for the management of advanced cases together form the Achilles heel for oncologists. Therapeutic strategy in NETs is multidisciplinary and includes surgery, interventional radiology and medical treatments such as somatostatin analogues, interferon, chemotherapy, new targeted drugs and peptide receptor radionuclide therapy (PRRNT) with radiolabeled somatostatin analogues. NETs usually overexpress somatostatin receptors on their cell surface, thus enabling the therapeutic use of somatostatin analogues, one of the basic tools for NETs. Ooctreotide therapy is most commonly used for palliative/symptomatic treatment of functional NETs; however, it depends on the confirmed presence of somatostatin receptors (sstr) on tumor. Similarly, the principle of PRRT using radiolabelled somatostatin analogs depends upon over-expression of sstr on NETs. The conventional imaging modalities like CT, MRI and USG provide excellent morphologic information, but frequently miss the localization of the primary tumor. A recent study showed a 59% detection rate of unknown primary NET (CUP-NET) by \( ^{68}\text{Ga} \) DOTANOC receptor PET/CT (12). It is a known fact that metabolic / molecular events precede morphologic changes by days to months. The functional information provided by PET/CT along with the possibility to do semi quantitative / quantitative evaluation has resulted in the conceptualization of a ‘tailored regime’. Also, the state of the art PET/CT, apart from providing functional information about the whole body in one sitting, makes it possible to perform diagnostic CT wherever needed and give vital information regarding the morphology of NET - keeping in mind that not all the tumors are sstr positive.[1,2] The high success of octreotide scintigraphy using \( ^{111}\text{In} \) labeled octreotide (Octreoscan) encouraged the development of positron emitter based sstr specific radiopharmaceuticals. \( ^{68}\text{Ga} \) is a radio metal and a positron emitter with a half life (T\( _{1/2} \)) of 68 min and produced from a \( ^{68}\text{Ge}/^{68}\text{Ga}-\text{generator} \) in a convenient, fast, “in-house” preparation.[3] The same peptides labeled with \( ^{68}\text{Ga} \) for diagnosis can be labeled with \( ^{177}\text{Lu} \) or \( ^{90}\text{Y} \) for radionuclide therapy,[4] a form of personalized treatment which has been given the term THERANOSTICS. The use of \( ^{68}\text{Ga} \) generators- first used by our center on a routine daily basis - may encourage a rapid increase of PET centers without cyclotron worldwide.

PRRNT – Basic Principles: As a consequence of the scintigraphic localization of neuroendocrine tumors with radiolabeled somatostatin analogues, therapeutic approaches with radiolabeled peptides were developed. The biological basis of PRRNT is the receptor-mediated internalization and intracellular retention of the radio peptide. Several clinical trials indicated that PRRNT with radiolabeled somatostatin analogues is among the promising newly developed targeted tools in neuroendocrine tumors.[3] Peptide receptor radionuclide therapy (PRRNT) can deliver radiation doses to tumors, which are adequate to achieve volume reduction or even cure. Initial studies were performed with high doses of the radiopeptide \([^{111}\text{In-DTPA}^6\text{Octreotide}] \). Objective responses were rare or questionable due to the short range (nanometers to micrometers) of the emission and therefore the short tissue penetration of the emitted Auger electrons. The radiopeptides that have been proven effective and which have been extensively studied are the \( ^{90}\text{Y} \) labeled peptide - \([\text{DOTA}^6, \text{Tyr3}]-\text{octreotide (DOTATOC)} \) and the \( ^{177}\text{Lu} \) labeled peptide \([\text{DOTA}^6, \text{Tyr3}]-\text{octreotide (DOTATATE)} \).[5] Our group was the first to use also \( ^{90}\text{Y} \) DOTATATE and in a large patient group \( ^{177}\text{Lu} \) DOTATOC. We also pioneered the use of \( ^{90}\text{Y} \) and \( ^{177}\text{Lu} \) DOTATATE in sequence (DUO-PRRT) and the concurrent use of \( ^{90}\text{Y} \) and \( ^{177}\text{Lu} \) octreotide analogues (TANDEM-PRRT) as well as the intra-arterial use of \( ^{90}\text{Y} \) DOTATATE and DOTATOC. DOTATATE has a nine-fold higher affinity for the somatostatin receptor subtype 2 compared to...
DOTATOC. In a preliminary report, 35 patients with neuroendocrine gastroenteropancreatic tumors were treated with escalating doses of $^{177}$Lu DOTATATE, resulting in complete and partial responses in 38% of patients. No serious side-effects were observed. In addition, $^{177}$Lu DOTATATE significantly improved the global health/status of life and various function and symptom scales in patients with metastatic gastroenteropancreatic tumors.

Due to their marked radiosensitivity, the kidneys are the critical organs in PRRT. Proximal tubular reabsorption of the radiopptide and the subsequent retention in the interstitium results in renal irradiation. Given the high kidney retention of radiopptides, positively charged molecules, such as L-lysine and/or L-arginine, are used to competitively inhibit the proximal tubular reabsorption of the radio peptide. Based on the animal experiments of the groups in Rotterdam and Amsterdam, our group has pioneered the clinical use of gelofusine in addition to amino acids for kidney protection. Cumulative and per-cycle renal absorbed dose, age, hypertension and diabetes are considered as contributing factors to the decline of renal function after PRRT.

Besides renal toxicity, bone marrow involvement must be considered although it appears not to be a principal dose-limiting factor. Acute hematological toxicity is not uncommon, especially after $^{90}$Y-labeled peptide therapy, and the possibility of a mild, but progressive impoverishment in bone marrow reserves has to be considered in repeated cycles. In addition, myelodyplastic syndrome (MDS) or overt leukemia may develop in patients receiving high bone marrow doses, especially in those previously treated with alkylating agents.

The challenge for internal radiation therapy is to deliver the highest possible dose to the tumor while sparing normal organs from damage. In addition, the inter-individual differences in dose delivery should be considered, particularly on the account of varying metabolism or receptor density in organs and tumor lesions. This makes individual patient dosimetry absolutely necessary in PRRT.

The Bad Berka Experience: $^{90}$Y DOTATOC (in Germany, the first patient was treated by myself in July 1997) and/or $^{177}$Lu DOTATATE (in use in our centre since 2004) as well as other radiolabeled somatostatin analogues like $^{90}$Y DOTATATE, $^{177}$Lu DOTATOC and $^{177}$Lu DOTANOC have been applied alone or in combination over the last years at the Bad Berka Neuroendocrine Tumor Center (BBNETC). The clinical indication was established by a multidisciplinary tumor board in patients with progressive neuroendocrine tumors, non-responsive to octreotide/interferon treatment or chemotherapy. $^{177}$Lu DOTATATE was predominantly used for smaller metastases or in patients with impaired renal or hematological function. Our group was the first to systematically use $^{177}$Lu and $^{90}$Y consecutively in the same patient (DUO-PRRNT). Over 3,300 treatment cycles in > 1,000 patients have been performed up to now.

Data analysis in patients with long term follow-up: 454 patients (mean age 59.1 years, 248 male, 206 female) received a total of 1,303 treatment cycles (mean activity 4.1 GBq, min. 1.05 GBq, max. 7.5 GBq per cycle, time between cycles 3 to 6 months). Number of patients/cycles: 111 pts/1 cycle; 106/2; 74/3; 75/4; 42/5; 23/6; 9/7; 1/8. For kidney protection, patients were well hydrated and received an L-lysine/L-arginine solution infused intravenously for 4 hours beginning 30 minutes before PRRT. Patients were selected based on high SST-R expression on $^{68}$Ga somatostatin receptor PET/CT. Before each new treatment cycle, restaging was performed by morphologic (CT/MRI) and molecular imaging ($^{68}$Ga DOTA-NOC PET/CT, in selected cases also FDG or fluoride PET/CT), blood chemistry and tumor markers (Chromogranin A, serotonin, specific hormones). Renal function was serially determined by Tc-99m MAG3 scan/clearance (TER) and by Tc-99m DTPA/GFR measurements. Tumor Dosimetry (MIRD/OLINDA) was performed after PRRT (using $^{177}$Lu DOTA-TATE). All data were entered in a structured ACCESS database (284 items/patient).

Tumor response in patients with NETs of non-pancreatic origin and pancreatic NET (pNET) after a mean follow-up of 2 years was as follows: Complete remission (CR), partial remission (PR), minor response (MR) after 3 cycles (progressive disease before) was seen in 52% of patients with pNET (48% in other non pancreatic NET); disease was stabilized in 39% of pNET as compared to 45% in non pancreatic NET. Objective tumor responses (including improvement of clinical symptoms) were seen in 93% (in 91% of pNET) of the patients. Significant hematological toxicity (mainly anemia, rarely neutropenia, and thrombocytopenia) occurred in less than 15% of all patients. MDS developed in 5 patients (all of them received also chemotherapy before). End stage renal insufficiency was not observed in any of the patients with normal kidney function before PRRT. In most patients receiving $^{177}$Lu DOTATATE alone (n=417 cycles), serum creatinine and TER/GFR did not change. Therefore, the probability and magnitude of renal toxicity can be significantly reduced when PRRT is administered in fractionated doses in patients without any preexisting risk factors and under appropriate nephroprotection. Risk factors include chemotherapy, diabetes mellitus, hypertension, Hedinger’s syndrome, and cachexia.

Another recent analysis of 416 patients (all NET subtypes) treated at the BBNETC showed a median overall survival from the time of first diagnosis of 210 months (Rotterdam data 128 months) and a median survival after 1st PRRT of 59 months (Rotterdam data 46 months). This experience confirms an earlier report, about overall survival benefit.
**Future Directions:** These include: DUO-PRRNT, TANDEM-PRRNT (administration of 177Lu and 90Y labeled sstr analogues concurrently on the same day), Intra-arterial PRRNT (for improved dose delivery to liver metastases). Combined PRRNT (in combination with other treatment modalities) these include: (a) Transarterial chemoembolization (TACE), selective internal radiation therapy (SIRT), radiofrequency ablation (RFA) (b) Chemotherapy (e.g. use of Capectabine, Doxorubicin) (c) Kinase inhibitors (e.g. Sunitinib, Sorafenib, Everolimus and others) and (d) Antibodies

**Summary:** PRRNT is highly effective in the management of NETs, even in advanced cases and lends a benefit in overall survival from time of diagnosis, of several years. There is a significant improvement of clinical symptoms and excellent palliation can be achieved. In patients with progressive neuroendocrine tumors, fractionated, personalized PRRNT with lower doses of radioactivity given over a longer period of time (Bad Berka Concept) results in good therapeutic responses. By this concept, severe hematological and/or renal toxicity can be avoided and the quality of life can be improved. Sequential (DUO) and concurrent (TANDEM) PRRNT are more effective in progressive NETs then using either radionuclide alone.

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**O-043**

**Ga-68 Imaging in Clinical Practice - The Indian Experience**

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**Aim:** To review the Indian experience with Ga-68 imaging.

**Materials and Methods:** Data was collected on Ga-68 scans performed at 3 centres in India with the facilities available for somatostatin receptor PET-CT imaging, with reference to number of scans and acquisition and reporting protocols and encountered difficulties and spectrum of cases.

**Results:** 3 centres in India: AIIMS (New Delhi), BIO (Bangalore) and Jaslok Hospital (Mumbai) routinely perform Ga-68 somatostatin receptor PET-CT since 2007. Approximately 1536 Ga-68 somatostatin receptor PET-CT scans have been collectively done in India to date. (881 AIIMS, 465 BIO, 190 Jaslok). Ga-68-DOTATE is the main agent used at Jaslok while Ga-68-DOTANOC is used at AIIMS and BIO. Tracer activities range from 500uci to 3 mci. Scanning was performed at 60 minutes post injection (range 30-90 min). Mostly whole body diagnostic CT scans with oral and i.v. contrast were obtained along with the PET acquisition; each scan taking 20-25 min. Patient was off long acting somatostatin analogues for at least a month prior to scanning. Majority of the scans were non

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functioning neuroendocrine tumors (41%) carcinoids (27%), insulinomas (12%), and pheochromocytomas/neuroblastomas (17%). Good to excellent quality images were obtained.

**Summary:** Ga-68 somatostatin receptor imaging has proven very useful in diagnosis and management of a wide spectrum of neuroendocrine neoplasms in Indian setting.

**O-044**

**Ga-68 DOTA TATE Imaging and PRRT in South Africa**

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Abstract not available.

**O-048**

**Combined Modality Radiopeptide Therapy of Neuroendocrine Tumors**

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Virtually no malignancies have been cured using single modalities of treatment (Kvols). Australian centres have more than a decade of experience of radiopeptide therapy of NET using $^{90}$Y-octreotide, $^{111}$In-octreotide and $^{177}$Lu-octreotate. Over the past 5 years addition of radiosensitizing chemotherapy with capecitabine and temozolomide at Fremantle Hospital has improved objective response, particularly in pancreatic primary, disseminated well-differentiated progressive unresectable gastro-entero-pancreatic (GEP) NETs. Radiopeptide therapy of gastro-entero-pancreatic neuroendocrine tumors (GEP NETs) using 4 cycles of 7.4 GBq $^{177}$Lu-octreotate as a single agent achieved ORR 46%, CR 2%, PR 28%. Combination with capecitabine radiosensitizing chemotherapy in patients with progressive disease did not improve the PR rate, but achieved stabilization of disease in 94% of GEP NET patients without increase in toxicity. Addition of temozolomide to the capecitabine and $^{177}$Lu-octreotate shows early promise, particularly for pancreatic NETs and preliminary results show PR in half the treated patients with minimal increase in transient myelosuppression. In particular, partial response in pancreatic NETs approaches 90%. A phase I study of standard 4 cycles of 7.8 GBq $^{177}$Lu-octreotate radiopeptide therapy with everolimus biotherapy commenced at Fremantle Hospital in May 2011 and our early experience will be presented.

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**O-049**

**Peptide Receptor Radionuclide Therapy with Radiolabelled Somatostatin Analogues: The Milano Experience**

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Peptide receptor radionuclide therapy (PRRT) with radiolabelled somatostatin analogues, $^{90}$Y-DOTATOC and $^{177}$Lu-DOTATATE, has been experimented in neuroendocrine (NETs) and non-neuroendocrine sst$_2$-positive tumors for more than 15 years. PRRT can deliver significant absorbed doses to tumors, able to cause volume reduction, as reported in published studies. Our preliminary dosimetric studies showed that the kidneys are the critical organs in PRRT and that bone marrow toxicity should be also taken into consideration. Later on, our phase I escalating studies of $^{90}$Y-DOTATOC, with dosimetric analysis, with and without renal protection with amino acids, showed no major acute reactions up to an administered dose of 5.55 GBq per cycle. Reversible grade 3 haematological toxicity was found in 43% of patients injected with 5.18 GBq, which was defined as the maximum tolerated dose per cycle. Between 1997 and 2002 our group treated 141 patients affected mainly by NETs, with a cumulative activity of 7.4-26.4 GBq of $^{90}$Y-DOTATOC, divided into 2-16 cycles, administered 4-6 weeks apart. Objective response rate was 26%. Disease stabilization was observed in 55% of the patients and disease progression in 18%. The mean duration of response ranged between 2 and 59 months (median 18). The majority of the patients who responded had gastro-entero-pancreatic NETs. We recently completed our phase I-II study with $^{177}$Lu-DOTATATE on 51 patients with mainly NETs, including bronchial, duodenum, ileum, appendix, rectum, pancreatic endocrine carcinomas as well as NETs of unknown origin,
paragangliomas and one case of meningioma. Patients were treated with 3.7-7.4 GBq per cycle up to a maximum cumulative activity of 3.7-29.2 GBq, divided in 1-7 cycles. No major acute or delayed renal or hematological toxicity occurred. Cumulative renal absorbed doses were 8-37 Gy (9-41 Gy bioeffective doses). Cumulative bone-marrow doses were <1.5 Gy. Thirty-nine patients were progressive at enrolment. Partial and complete responses occurred in 15/46 (32.6%) assessable patients. Median TTP was 36 months. Overall survival was 68% at 36 months. Non-responders and patients with extensive tumor involvement showed lower survival. Regarding safety, our group has been committed in evaluating the dosimetric and clinical aspects toxicity to the target organs, the kidneys, primarily, and the bone marrow. The long-term evaluation of renal parameters in patients undergone to Y-DOTATOC or Lu-DOTATATE therapy and dosimetric studies, showed that patients with risk factors for late renal toxicity showed a lower renal absorbed dose threshold (28 Gy) than did those without risk factors (40 Gy). The evaluation of the haematological toxicity with the increase of the bone marrow dose, showed, for Y-DOTATOC, a mild but progressive impoverishment of the bone marrow reserves. As to the commonly observed G2-3 lymphocytic toxicity, we studied the course of lymphocyte subsets after Y-DOTATOC and Lu-DOTATATE. We demonstrated that lymphoid toxicity mainly affected B-cells, particularly after Y-DOTATOC. This phenomenon was transient and resolved completely at the end of the 90-day follow-up. Due to the selective targeting of B-cells, no increase in infections is normally observed after PRRT. These findings open interesting perspectives in the treatment of B-cell lymphoproliferative disorders. Presently our group is evaluating the effect of combination therapies, specifically of Lu-DOTATATE plus the radiosensitizer capecitabine, administered with a metronomic schedule, in patients with aggressive NETs. Our group is developing phase II protocols evaluating the therapeutic potential of both Y-DOTATOC and Lu-DOTATATE and the optimal schedule in terms of dosage per cycle and interval between cycles. In the future, phase III protocols comparing Y-DOTATOC versus Lu-DOTATATE and PRRT versus conventional therapies will help clarify the position of PRRT in the therapeutic algorithm of NETs.

O-050

Meta-analysis of Radionuclide Therapy in NETs

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Aim: To attempt to collate and compare the results of studies using radionuclide therapy in patients with neuroendocrine tumors.

Materials and Methods: A retrospective review was performed of the published literature (and data from our own institution) using PUBMED to identify those studies reporting results of radionuclide therapy with I-131 mIBG, Y-90 DOTATOC, Y-90 DOTATATE and Lu-177 DOTATATE in patients with proven advanced neuroendocrine tumors. Data included, where available, the number of patients treated, the cumulative activity given, the type of tumors treated, the radiological response rate, progression free and overall survival and symptomatic response rate.

Results: Results of treatment in 2616 patients was available. Direct comparison was difficult, as data was not collected in a uniform way. Radiological response rate ranged from 23% to 30% but the CR rate was only 0-2%. Treatment failure ranged from 9% to 27%. Symptomatic responses varied, ranging from 34% to 77%. Several authors noted with a variety of agents that overall survival correlated better with symptomatic response than with response. The median OS was calculated to be 46 months using or I-131 mIBG and 44 months using Lu-177 DOTATATE. For 2 of the agents (Y-90 DOTATOC and Y-90 DOTATATE), the data from the majority of studies published had not yet reached a value for median overall survival.

Conclusion: There is no radionuclide therapy agent that was clearly better than others and use may be limited by cost and availability. However radiological response rates of up to 30% and symptomatic relief rates of up to 77% and medical overall survival of >44 months all appear achievable with these techniques.

O-052

Training Nuclear Medicine Physicians Foundation and Ideal Model

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Nuclear Medicine is a unique specialty which is not yet appreciated as an important component of modern medicine and carries the potential of significant development of medical care in general. Decision makers, medical strategists, some practicing physicians as well as some nuclear medicine professionals are not fully aware of such fact. Consequently proper training of future specialists in this field is a challenge to prepare generations for the future struggle to continue develop this filed and meet the challenges imposed by both rapid changes in the field, policies and awareness.
Usefulness of SPECT/CT in Radionuclide Tumor Therapy

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Introduction: In a way comparable with the combined use of PET and CT, hybrid imaging of SPECT using single photon tracers in combination with low dose CT is a recent adjunct, which allows better detection and localisation of diseases. Where PET/CT is not available, SPECT/CT is a relatively inexpensive alternative, which is associated with improved diagnostic sensitivity and accuracy over planar scintigraphic procedures. Moreover, currently the choice of commercially available single photon tracers is greater than that of positron emitting radiopharmaceuticals. A SPECT/CT scan is generally added to planar scintigraphy in selected cases using a variety of single photon radiopharmaceuticals for a great variety of indications, e.g. scintigraphy of the thyroid and parathyroid, the heart, lungs, brain, kidneys, bone, as well as imaging of infection, bleeding, lymphatic drainage (sentinel lymph node biopsy) and tumors using tumor seeking radiopharmaceuticals, either for diagnostic imaging or for radionuclide therapy.

SPECT/CT imaging procedure: Following the administration of radiopharmaceutical and a waiting time, which is dependent on radiopharmaceutical used, first planar scintigraphy is performed, either as a total body procedure or with spot views. On the basis of the scintigram it is determined if additional SPECT/CT is required/meaningful and, if so, the area of interest for SPECT/CT acquisition is selected. First SPECT of the selected area is performed. Subsequently a X-topogram of the area of interest is made, followed by a spiral CT-scan, either with low dose (suffices in most cases) or with diagnostic dose and i.v. contrast. Then SPECT image reconstruction is performed, both uncorrected and attenuation corrected, and the corrected images are fused with the CT slices, resulting in additional series of transaxial, coronal and sagittal SPECT/CT fusion images. 3D Volume display and stacking of transaxial SPECT/CT slices to form 3D Volume rendered rotational images may also be helpful and illustrative for the referring physician.

Tumor imaging: For tumor imaging a great variety tumor seeking radiopharmaceuticals may be used e.g., 201Tl-chloride, 67Ga-citrate, 99mTc-sestamibi, 99mTc-pentavalent DMSA, 123I-MIBG, 111In-pentetreotide, 131I-iodide, 131I-MIBG and radiolabelled antibodies. Adding SPECT/CT may not only have advantages over planar scintigraphy in terms of greater sensitivity and better localisation of lesions, but may also be the prelude to therapeutic use of some of these radiopharmaceuticals (selection of patients, dosimetric assessment). Clinical examples will be demonstrated, in which SPECT/CT, using specific tumor seeking radiopharmaceuticals is actually superior to PET/CT, when the relatively specific tracer 18F-deoxyglucose (FDG) is used. And in recent years the imaging quality of SPECT/CT has significantly improved, so that SPECT/CT fusion images can well be compared with PET/CT.

Tumor therapy: Although several of the radiopharmaceuticals used for radionuclide therapy have less favourable characteristics for scintigraphic imaging, this is much less of a problem in SPECT/CT. Not only does the higher administered dose provide better statistics for the SPECT reconstruction (compared to a diagnostic
dose), also the poorer resolution is much less obvious, thanks to the SPECT images being fused with CT. As a result both the detection and the localisation of tumor sites targeted by the therapy, as well as the assessment of its distribution within/around the tumor, are significantly improved. Following $^{131}$I-ablation therapy in differentiated thyroid carcinoma $^{131}$I-SPECT/CT makes it easier to distinguish normal residual thyroid tissue from lymph node metastases and may detect small $^{131}$I-avid metastases easily missed on planar post-ablation scintigraphy. Moreover, the CT-component of this technique may reveal additional tumor localisations, which do not concentrate $^{131}$I and would require a different treatment modality. In cases of non-$^{131}$I-avid thyroid tumors, treated with $^{131}$I-iodide on the basis of the thyroglobulin level only, SPECT/CT may provide the explanation why some patients respond favourably to this treatment and others do not. In palliative therapy of painful skeletal metastases using $^{153}$Sm-EDTMP, SPECT/CT may demonstrate which type of targeting has occurred: when concentrated in the periphery of a centrally cold (osteolytic) metastasis, this treatment is likely to be useful for pain palliation only. But, if the radiopharmaceutical is diffusely distributed within the (usually osteosclerotic) metastases, there may be an antitumor effect in addition to the pain palliation. In patients with metastatic neuroendocrine tumors pretherapy $^{123}$I-/ $^{131}$I-MIBG and $^{111}$In-octreotide scintigraphy with SPECT/CT may indicate which targeting mechanism will be the prominent one and can provide the key to therapy. The successful tumor concentration and retention may be elucidated by posttherapy SPECT/CT after treatment with either $^{131}$I-MIBG or $^{90}$Y-/ $^{177}$Lu-Dotatate. Similar uses of SPECT/CT are appropriate in radioimmunotherapy and to monitor the correctness of positioning of the catheter in i.a. radionuclide therapy of the liver, by excluding deposition of the radioactive particles in other organs and estimating the degree of shunting to the lungs. 

Conclusions: SPECT/CT is a valuable adjunct to many planar nuclear medicine procedures, providing improved detection and localisation of disease, and is superior to SPECT only. In radionuclide tumor therapy SPECT/CT may provide more insight into the effectiveness of the targeting and explain the observed response.

O-057
The Utility of PET in Intensity Modulated Radiotherapy Planning
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Molecular imaging with PET/CT in radiotherapy allows better tumor staging, modification of treatment fields, localised symptom control and therapy response evaluation. There is a clear dose-response relationship between radiation dose and biochemical tumor control rates. Intensity modulated radiotherapy planning is a strategy that has been proposed to enable the delivery of high radiotherapy doses without giving an unacceptably high risk of toxicity. There will be a review of the current literature and the emerging role of PET in this setting, including the role of new pharmaceuticals in this arena.

O-058
Prognostication in Radionuclide Therapy
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Radionuclide therapy has a special and established role in the management of various benign and malignant conditions. While the therapy usually fits in very neatly in well evidenced patient management algorithms, the question of alteration of prognosis due to the treatment itself has not been studied in detail. In this presentation, I would like to review the role of patient selection, the role of pre treatment assessments and the treatment algorithms which ultimately influence prognosis. These factors usually have a significant effect on the prognosis in addition to the disease status and histology itself. Radionuclide therapy for thyrotoxicosis, thyroid ablation for thyroid carcinoma and targeted radionuclide therapy for neuroendocrine tumors will be discussed in more detail. Relevant international consensus guidelines will be reviewed in the context of the conference.

O-059
The 3-D Dosimetry in Radionuclide Therapy Based on 4-D SPECT/CT Acquisition
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Peptide receptor radionuclide therapy (PRRT) is already a part of current Scandinavian guidelines in treating
Abstracts

neuroendocrine tumors. Lu-177 and Y-90 labeled somatostatin analogs, to which DOTATOC, DOTANOC and DOTATATE belong, are most commonly used and have turned out to be effective. For clinical routine, we have developed a system for dose calculation and for predicting therapy doses based on serial pre- and post-therapeutic scanning. In pre-therapy scans, approximately 0.2 GBq Lu-177-DOTA-FCFWLTCTate was injected for serial imaging at 1, 24 and 72 and/or 168 hrs using amino acid kidney protection (25 g L/l, 25 g R/l). Similar conditions were applied for post therapeutic scanning after receiving 6.6-7.8 GBq of the Lu-177-labelled compound. Both OLINDA and our own software was used for actual dose calculation. Tumor to background –ratios based on SPECT/CT in liver varied from 4:1 to 15:1. The tumor doses varied from 2.4 to 110 Gy and normal organ doses in kidneys 2.4 -6.0 Gy, normal liver 2-20 Gy, spleen 1.5-16.4 Gy per cycle using post-therapeutic scans. The highest tumor dose was typically obtained in the first cycle. Our own software is a voxel-based system, alignment for voxel half-life calculation was made by NM fusions. The OLINDA software and our programme gave similar normal organ doses, whereas tumor doses could be calculated in a more detailed manner using the 3-D programme. In dose planning pre-therapeutic scanning can predict critical organ doses, in some organs with a slight overestimation, e.g. kidney and spleen. Tumor dose was similar in both pre-therapeutic and post-therapeutic scans using our special software. Because of a precise voxel based approach, bone marrow dose could also be predicted and verified. Thus dose planning in advance, like as part of external beam therapy, requires new tools. No practical tool for PRRT does exist, this might be one. Basic problem is the possible change in radio- pharmacokinetics when the activity comes 40-fold and the specific activity remains the same. In a multicenter study, this extrapolation factor may be calculated in an appropriate manner. Preliminary, we also have studied the doses in combinatorial therapies, this gives a possibility to plan therapy trials based on actual tumor dose.

O-060

Dosimetry in Solid Tumors - Does it Have Any Use?

J. R. Buscombe

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Dosimetry to many nuclear medicine physicians is great when done by someone else. However the reason dosimetry is important is that it can be used to predict and reduce the probability of toxicity and also hopefully to enhance efficacy. Dosimetry is at its best when it is done along with treatment preparation. A good example for this was the IAEA project using Re-188 lipiodol where a dosimetric calculation of lung dose was used to reduce the chance of toxicity and indeed toxicity was minimal for that study. However to do dosimetry well requires time patience and money. Often the patient needs to be imaged just after the therapeutic treatment is given and then for several days. To get tumor radiation doses, SPECT, or better SPECT-CT, is useful. Sometimes PET can be used to predict radiation dose for example by the use of Y-86 DOTATOC PET to predict the dosimetry of Y-90 DOTATOC therapy. Most work has been directed towards reducing toxicity often by looking at the dose limiting organ such as lung, kidney or bone marrow. More recent work however has looked at how dosimetry can be used to optimise treatment. The truth is dosimetry will be done when it can be shown to be useful for predicting outcomes as well as reducing toxicity. There also needs to be greater standardisation of methods before it can be used widely.

O-061

Current Knowledge of FET use in PET

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The standard diagnosis of glioma is done by MRI and CT, standard treatment consists of surgery and radiation therapy (RT) with concomitant adjuvant chemotherapy. However, a presence of tumor and a real measure of tumor extension in gliomas is quite difficult with either modality. Unfortunately, the demonstrated benefit of this way does not extend to cure for the vastmajority of patients. As the fast surgery and RT are the basics of the treatment strategy, defining the precise tumor volume (borders) is also of paramount importance. In the particular case of recurrent gliomas, MRI was found to have a low specificity to distinguish between side effects of therapy and tumor recurrence corresponding to only about 50%. PET with radiolabeled amino acids or amino acid analogs may help to overcome the noted limitations of morphologic imaging and has proven to be useful in the diagnostic work-up of brain tumors. O-(2-18Ffluoroethyl)- L-tyrosine (FET) [Figures 1 and 2] is a promising 18F-labeled amino acid analog that is taken up by the transport system L but is not incorporated into proteins.
The clinical studies have proven that $^{18}$F-FET PET identifies low- and high-grade gliomas and is able to discriminate these from benign lesions with very high probability. The possible pathways for the transport of neutral amino acids into the cells are described as three major systems: A, ASC and L. Systems A and ASC serve mainly for the uptake of amino acids with short, polar or linear side chains. Branched and aromatic amino acids enter the cells mainly by system L. For L-tyrosine, the system L was determined as the main transport system in melanoma cells. Synthesis of this tracer is quite simple and is going in the nucleophilic way thus enabling mass production in the typical PET laboratories.

Typically injected activity of FET varies between 150 -370 MBq. It was demonstrated in preliminary series that the maximal FET uptake in tumor tissue was reached at 20 min post injection. Time-activity curves for normal brain tissue showed a plateau after 20-30 min p.i.; thereafter, tumor to background ratios remained almost stable. Therefore, the quantitative evaluation in the present study was based on a time period between 30 min and 60 min. In some clinical studies FET sensitivity varies between 90 - 100%, specificity 95- 100%, giving similar accuracy, positive predictive value and negative predictive value. In comparison to MRI the a sensitivity for the detection of tumor tissue was similar but a specificity of MRI only 53%. Combined use of MRI and FET PET yielded a sensitivity of 93% and a specificity of 94%. To properly assess the border between tumor and normal tissue the different ratios were introduced but the most accurate results were achieved using 1.5 coefficient. There was no uptake of FET in acute and chronic inflammation and astrogliosis. Also after radiotherapy one could not observe increased uptake in the treated area. Combination of FET with MRI yielded very high sensitivity in case of small round brain lesion. Possibility to differentiate low and high grade tumors was confirmed and using two time point acquisition we were able to classify these two groups of gliomas. In conclusion FET PET is able to diagnose recurrence, stage the tumor for neurosurgery, monitor treatment response and help in the diagnosis of primary lesion.

O-062

The Tracer Principle: From de Hevesy’s Cup of Tea to the Secret Services

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Through his life's work George de Hevesy is regarded as the father of nuclear medicine. In 1911 he took up a position at the Manchester Physics Laboratory in England working under Ernest Rutherford. The story is often told that while drinking a cup of tea on a spring day in 1913 de Hevesy expressed a desire to determine the fate of the individual water molecules contained in the tea he consumed. When Harold Urey provided de Hevesy with several liters of 0.6% deuterium oxide (heavy water) in 1933, he was presented with the means to discover the fate of tea he drank. Whether or not de Hevesy made tea from it is not recorded, but he and a co-worker Erich Hofer, drank the heavy water and after sampling urine and other excreta revealed that half of the body’s water turned over over every 9 days and estimated the body’s water content at 43 liters. This work represents the first application of isotopic tracers in medical research and the first use of isotopic dilution in the biological sciences. Following this and other early work, the use of radioactive tracers has been applied not only in routine nuclear medicine procedures but also for a broad range of biological, agricultural and industrial applications. However, until recently it has not been widely known that radioactive tracers have been employed for more sinister purposes of security and surveillance. Since the fall of the Berlin wall in 1989 evidence has emerged that the Ministry for National Security (MfS) in the former German Democratic Republic used radioactive materials such as adhesive foils and squirtable liquids containing radionuclides such as Ag-110m, Na-24, Fe-59 and Co-60. These were used to mark papers, bank notes, passports, pens, bags, and suitcases. In addition items of clothing, car tires and vehicles were tagged to monitor the movement of individuals and cars. Security officers were given radiation detectors to wear under clothing so that they could be alerted to the movement of potential items and people who were under surveillance.
Although murder by poisoning with radioactivity has been well publicized, the use of radioactive tracers by secret services for surveillance tracking and monitoring is not common knowledge.

O-063

Intraoperative Avidin Biotin Procedure

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Background: Breast conservative surgery (BCS) plus external beam radiotherapy (EBRT) is considered the standard treatment for early breast cancer. We have investigated the possibility of irradiating the residual gland using an innovative nuclear medicine approach named IART (Intraoperative Avidination for Radionuclide Therapy). Aim: The objective of this study was to determine the optimal dose of avidin with a fixed activity (3.7 GBq) of 90-Y-biotin, in order to provide a boost of 20 Gy, followed by EBRT to the whole breast (WB) at the reduced dose of 40 Gy. Local and systemic toxicity, patient quality of life, including the cosmetic results after the combined treatment with IART® and EBRT, were assessed.

Materials and Methods: After tumor excision, the surgeon injected native avidin diluted in 30 ml of saline solution into and around the tumor bed. Patients received one of three avidin dose levels: 50 mg (10 pts), 100 mg (15 pts) and 150 mg (10 pts). Between 12 to 24 hours after surgery, 3.7 GBq 90Y-biotin spiked with 185 MBq 111In-biotin was administered intravenously. Whole body scans and SPECT images were performed up to 30 hours post injection for dosimetric purposes. WB-EBRT started after 4 weeks from IART® boost. Local toxicity and quality of life were evaluated. The results of the follow-up were also reported.

Results: 35 patients were evaluated. No side effects were observed after avidin administration and 90Y-biotin infusion. The avidin dose level of 100 mg resulted the most appropriate in order to deliver the radiation dose required (19.5 ± 4.0 Gy) to the surgical bed. At the end of IART® no local toxicity occurred and the overall cosmetic result was good. The tolerance to reduced EBRT was also good. The highest grade of transient local toxicity was G3, which occurred in 3/32 pts after the completion of WB-EBRT. The combination of IART®+EBRT was well accepted by the patients, without any changes in their quality of life. No local recurrences occurred after 20-44 month of follow-up (media 35.7, median 36). One patient underwent breast conservative surgery for a contralateral tumor after 15 months.

Conclusions: These results support the hypothesis that IART® may represent a valid approach to accelerated whole breast irradiation after BCS and led us to pursue further objectives. We have designed a comparative randomized trial aiming at demonstrating by 3D dosimetry, the reproducibility of the IART approach compared to dosimetry of IORT + EBRT.

O-064

Positron Emission Tomography in Breast Cancer

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Breast cancer is 16% - 22.8% of all female cancers and is responsible for high mortality rate. The incidence worldwide varies in relation with the degree of industrialization of the regions, with highest prevalence in developed countries. Early diagnosis decreases morbidity and mortality, for this reason most of the work has been focused to develop programs for early detection of disease. However, in spite of all efforts 10-15% of cancers fail to be detected and remain hidden in normal but dense breast tissue. Mammography is the technique of choice for breast cancer screening and its established use has reduced mortality by 30% in the USA statistics, but its sensitivity decreases dramatically from 98% in fatty breasts to 48% in dense breast, in some series. Ultrasound improves the specificity especially in cases of cysts and dense breasts, helping to characterize the lesions but only 30% of lesions carried to biopsy are true positives.

Once breast cancer is diagnosed, it is critical to establish the extent of the disease to define the therapeutic strategy. The size and extent of breast cancer are often underestimated by physical examination and mammographic findings with or without ultrasound. Molecular imaging provides information about neo angiogenesis (MRI), tumor metabolites (MRS), increased number of mitochondria (MIBI) and increased metabolism of the cells (PEM) and it allows diagnosis, treatment and follow-up. Positron Emission Mammography (PEM) use glucose labeled with F18 (18 F- FDG), based on the increased tumor metabolism and avidity by glucose. Images are acquired in the same projections as those of conventional mammography (cranio-caudal, mediolateral oblique, lateral, axillary) [Figure 1]. The interpretation is simple due the mild uptake of normal breast tissue. This technique is able to detect lesions of 1.5 mm.
In the paper published by the group of Dr. Ber in 2006, doubtful or suspicious mammograms by 94 pts, PEM characterized the lesion with a sensitivity of 90% and specificity of 86%. More recently Dr. Schilling of Boca Raton, in January 2011, published a prospective study in 218 patients with breast carcinoma and evaluation with PET (whole body), PEM and breast MRI. They found that pre-menopausal women with dense breasts or on hormones support the sensitivity to detect lesions with PEM and MRI was equal, but to detect peri lesion lesions or multifocal lesions PEM was clearly superior. PEM and MRI equally detect invasive cancer, but PEM is more accurate to define a lesion as benign and has fewer false positives. The sensitivity and specificity of PEM is 85% and 74% vs MRI 98% and 48% respectively. PEM compared to the MRI has the advantage that is not affected by hormonal status or with dense breasts, no claustrophobia, no problem in patients with renal failure, no problem with metal implants or adverse reactions to contrast.

Disadvantages of PEM

- False-negatives: Lobular carcinomas, low metabolic activity, micro-mets.
- False-positives: Fat necrosis, papilloma, biopsy site / hematoma, granulation tissue, Inflammation.
- Higher whole body radiation relative to MR or mammography
- Anatomical constraints: Posterior axilla breast-
- Cost and availability

O-065

Radioimmunoscintigraphy and Radioimmunotherapy: The State of the Art

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Introduction: The concept of using autologous or heterologous antibodies for tumor detection and therapy dates back nearly 100 years. Attempts to treat cancer by passive specific immunotherapy were reported by Hericourt and Richet in 1985. It was in 1906, however, that Paul Ehrlich developed the concept of delivering therapeutic agents by immunologic means. He imaginatively described the antibodies as "magic bullets (that) seek out the enemy". Tumor antigenicity was recognized in 1929 by Witesbsky and in 1960 Bale et al. demonstrated tumor accumulation of heterologous specific antibodies. Bale also reported that antibodies could carry therapeutic doses of radionuclides to tumors. His observations led to the first human radiolabelled antibody studies. Following the pioneering work of these investigators, clinical applications of radioantibodies to tumors and other pathologic organs have been reported by many authors. The major breakthroughs in cancer detection by radioimmunoscintigraphy are summarized as follows:

- The use of monoclonal antibodies instead of polyclonal antibodies, resulting in more specific accumulation of the tracer and much higher target to non-target ratio;
- The selection of the most favorable target tumor marker and the best monoclonal antibody directed against this antigen;
- The use of new isotopes for imaging and treatment of cancer;
- The use of antibody fragments instead of intact antibody;
- The use of new imaging techniques and new instrumentation, such as single-photon emission computerized tomography (SPECT and SPECT/CT);
- New methods to increase the antibodies’ specific tumor targeting, such as the use of unlabeled antibody to bind the circulating free antigens. This can potentially prevent the radiolabeled antibody from reaching the tumor-bearing sites.

Recent advances: All but a small minority of the existing methods of tumor diagnosis are indirect, based on differences in tumor vascularity, x-ray absorption, ultrasound reflection, mass effect, hyper-metabolic activity or increased protein catabolism. Results are frequently nonspecific for tumors and confusion with inflammatory or vascular disorders is not uncommon.

Recent developments have spurred research in radiolabeled monoclonal imaging and therapy. Radioimmunodiagnosis offers a possible solution to these problems and also permits imaging of the entire body in search of unsuspected sites of tumor involvement. The significance of this method for therapy is even greater, since existing treatments are often ineffective or only partially or temporarily effective. RIS and RIT are not new techniques, but have progressed significantly in the last 10 years.

RIS advances: Every malignant tumor has been found to have specific cell-associated antigens that can be used as markers for a given type of neoplasm. Certain physical and biological parameters must be considered, however, in view of their relationship to tumor accretion of antibodies. Several newer
tumor-associated antigens that have been tried in clinical research for immunoscintigraphy include the pancreatic oncofetal antigen (extracted from fetal pancreas and pancreatic carcinoma), prostatic acid phosphatase originating in the ductal epithelium of the prostate, human milk fat globulin (HMFG), ferritin, and various other tumor-associated antigens (i.e., renal carcinoma, colon specific antigen, osteosarcoma, etc.).

**RIT advances:** Two RIT agents have been recently approved by the FDA for the treatment of B-cell Non Hodgkin’s Lymphoma and related conditions: 90 yttrium ibritumomab tiuxetan (Zevalin) and I-131 tositumomab (Bexxar). Both target the CD-20 surface proteins on normal and malignant B cells.

Some other advances of RIT for solid tumors include: Intracavitary RIT aims to limit toxicity and improving tumor targeting for: ovarian cancer glioma; peritoneal carcinomatosis of colorectal origin; early urothelial cell cancer; malignant pleural mesothelioma and effusion; is more effective in patients with small volume solid tumors. More advances of RIT of solid tumors include: nasopharyngeal carcinoma; metastatic CEA-producing malignancies; breast cancer. RIT of infections is still under investigation with reported good results for murine cryptococcosis, streptococcus pneumonia and viral HIV-1 infections.

**Summary:** Monoclonal antibody imaging presently appears to be both time-consuming and expensive, compared to CT and MRI. Antibodies can detect a tumor marker within a lesion, however, whereas the other methods detect only morphological alternations. Developments in antibody production, purification, fragmentation and labeling, combined with improvements in instrumentation and knowledge of the clinical and technical factors associated with radioimmunoimaging, may improve the reliability and availability of RIS. It is hoped that it will become established as a standard method for managing cancer and certain other benign disorders.

**O-066**

**Radioimmunotherapy of Non-Hodgkin Lymphoma with 131I-rituximab**

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Chimeric anti-CD 20 Mab may be easily and safely radiolabelled with Iodine-131 in a university hospital nuclear medicine laboratory for radioimmunotherapy (RIT) of non-Hodgkin lymphoma (NHL). 131I-rituximab provides safe, effective, practical, affordable and available RIT for patients with indolent NHL upon first presentation, or with relapsed or refractory disease or requiring consolidation of chemotherapy. More aggressive NHL such as Mantle Cell lymphoma, DLBCL or aggressive transformation may respond to non-myleoablative 131I-rituximab or RIT conditioning for marrow transplantation.

Patients with NHL who respond to 131I-rituximab RIT may be retreated upon relapse with expectation of renewed response without additional toxicity. Toxicity of the non-myleoablative 131I-rituximab RIT regimen is modest being self-limited myelosuppression and occasional hypothyroidism.

To determine the safety and efficacy of first-line 131I-rituximab radioimmunotherapy of previously untreated patients with advanced symptomatic follicular non-Hodgkin lymphoma (NHL) and to establish the durability of response we conducted a prospective Phase II study. Fifty patients presenting with follicular NHL over a 4 year period received a therapy activity of 131I-rituximab, predicated upon a fixed whole body radiation dose of 0.75Gy. Response was assessed by comparison of 18F-FDG positron emission tomography/CT (PET/CT) at study entry with that obtained 3 months post-therapy. Durability of response was determined by clinical follow-up and repeated PET/CT imaging. Complete remission (CR) was achieved in 78% of patients, partial response (PR) in 20% with an overall objective response rate (ORR) of 98%. Median PFS was not reached. No disease-specific death occurred during the median follow-up of 28 months.

Toxicity was limited to haematological grade 4 neutropenia occurring in 10% and thrombocytopenia in 10%. There were no episodes of bleeding or infection. Hypothyroidism was seen in 7 patients (14%). First-line radioimmunotherapy of follicular NHL with 131I-rituximab is safe and efficacious in follicular NHL and should be considered as an alternative treatment to chemotherapy-based regimens. Durable complete remission is achieved in three quarters of patients and there is potential for repeat radioimmunotherapy on relapse.

Radioimmunotherapy of indolent non-Hodgkin lymphoma (NHL) has achieved objective response rates (ORR) in clinical trials comparable with standard R-CHOP chemotherapy, but is relatively underutilized in routine practice. We have reported our ten year clinical experience in 142 consecutive patients who received Iodine-131 rituximab radioimmunotherapy for low grade, predominantly follicular, relapsed NHL (Blood 2011; 117(1):45-52). ORR of 67% with complete remission (CR) in 50% and median overall survival (OS) 32 months, matched the response rates in Phase II clinical trial of 131I-rituximab radioimmunotherapy and compares favourably with those reported for 131I-tositumomab or
Radioimmunotherapy (RIT) with PET/CT is limited by international guidelines. Release dose rates of less than 25 μSv/h at 1 m were attained within one week of therapy. Outpatient I-131-rituximab radioimmunotherapy of non-Hodgkin lymphoma with therapeutic activities between 1000 and 4500 MBq (mean 2290 MBq), predicated upon whole body radiation absorbed dose of 0.75 Gy, were studied. Their family members/carers and visitors wore TLD badges for the week during which the patients were confined to their home and contact with children and pregnant women was avoided. The median radiation exposure of carers and public is well within the limit permitted by international guidelines. Release dose rates of less than 25 μSv/h at 1 m were attained within one week of therapy. Outpatient I-131-rituximab radioimmunotherapy of non-Hodgkin Lymphoma is safe and effective.

O-067

Use of PET/CT to Monitor the Results of I-131 CHT-25 Radioimmunotherapy

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PET/CT has become a standard procedure for management of Hodgkin lymphoma (HL). It has been used for initial staging, restaging, monitoring during therapy, post-therapy surveillance in HL and a surrogate marker in new drug development. Recent attempts have been made to standardized role of PET/CT in clinical trials and their incorporation in assessing response both in interim imaging and end of conventional treatment studies. Evidence for monitoring response of lymphoma to Radioimmunotherapy (RIT) with PET/CT is limited and is predominantly related to targeted therapy in non-Hodgkin lymphoma patients. Currently, there are no standardized recommendations used for evaluation of response to RIT. Optimal timing for performing PET/CT after RIT in lymphoma patients has not been yet established. Studies evaluating response to RIT using International Working Committee (IWC) criteria demonstrated that PET/CT performed 6-8 weeks post RIT appeared to be reliable tool for response assessment. I-131 Basiliximomab, new radiolabelled antibody, is being developed for the treatment of HL in phase I trial. Response evaluation to RIT in refractory HL with PET/CT will be demonstrated.

O-071

The Value of Life and the Concept of Quality of Life: A Critical Examination of the Basic Principles for the Clinical Measurement of the Quality of Life

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The phrase „quality of life” presupposes that of „quantity of”, but is, however, more related to „value of” than to the former. Therefore, in the measurement of the „quality of life” not the available number of the supposed determinative indicatives like health and functioning, wealth and leisure, role and social contacts and the quantity of their availability, but rather the individual’s or group’s “satisfaction with life” („subjective wellbeing” -SWB) should play the central role. This reduces the concept of quality of life to that which it pragmatically refers to in daily clinical counseling und assessment, namely the “question of meaning”, in which the meaning of a particular or continued therapy is assessed in the light of the individual’s experience of “meaning in life” (fulfillment) and the physician’s understanding of “meaning of life” (value of life). Here we shall try to demonstrate how the physician’s understanding of the human life can influence his spontaneous and subjective assessment of the QOL of his patient needed in daily clinical attention to the patient. We shall discuss factors that expose the weaknesses of most standard QOLI (Quality of life Index) and try to suggest elements that could contribute to more objective measurements. Referring to well conducted scientific researches which prove that religion, because it can influence one’s attitude to suffering and life in general and by so doing improve or sustain his good SWB, can improve the quality of life of its adherents, we shall argue for the inclusion of religion as one of the significant variables in the measurement of quality of life. Finally, we shall try to demonstrate how in the areas of Oncology and Nuclear Medicine, the promises of currently experimented therapies compound...
the dilemma of the physician, who by conscience cannot easily discard these promises of new possibilities of saving life because of anticipated danger of reduced QOL.

O-072

Quality of Life From a Doctor’s Perspective: Review of Actual Clinical Data

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Quality of life (QOL) is an important outcome measure in the treatment of malignant tumors. The European Organization for Research and Treatment of Cancer EORTC QLQ-C30 has been adopted to measure QOL before starting treatment, as a baseline scan, and to compare it to post-therapeutic results. The assessment of global health, functional parameters, such as physical status, emotional and social status and symptomatic parameters, such as nausea or fatigue, are included in this evaluation. Multivariate analysis of influencing factors have shown that higher QOL scores can be pre-assumed, if the patient is in a partnership, does not experience financial impact as a consequence of disease and treatment, and has had higher education. Generally, patients show lower values for QOL scores with higher age. In cancer patients sources of satisfaction and self-esteem can be compromised. Fearfulness, therapeutic side effects, and the possibility of treatment failure and death are always present. These effects may affect health-related QOL, which includes both physical and psychological components. Thus, improvement of QOL is an important goal of oncologic treatment beyond and perhaps independent of the curative one.

This lecture will present data on routine QOL assessment in patients treated with radioisotopes at the Department of Nuclear Medicine in Innsbruck. Furthermore, we are going to review the data provided in the few available publications as well as data collected from other Nuclear Medicine centers.

We are going to focus our interdisciplinary discussion on neuroendocrine tumor (NET) patients and thyroid cancer patients (TCA).

NETs, which form a rare entity of malignant disease, are characterized by a high variation of biological behavior, are often diagnosed late in the course of the disease and often still do not reduce life expectancy drastically. Therefore, illness perception and the influence of treatment on the patients’ well-being becomes an important factor in treatment planning. Various QOL questionnaires and classification schemes have been adopted for NET patients, aiming to capture side effects in order to prevent them. This modular approach requires sensitivity to underlying changes in the patients’ status. Limited publications suggest that in symptomatic NET patients symptom control by long-acting octreotide or lanreotide analogs may improve QOL, regardless of the fact that tumor reduction is achieved in only a small percentage of patients. However, recent data from the PROMID study provide evidence that the median time to progression is longer in NET patients receiving these analogs. Publications of the Rotterdam and Innsbruck Universities have reported that NET patients treated by radiolabelled somatostatin analogs may show a stable QOL posttherapeutically. This finding seems to hold true not only for patients responding to peptide receptor related therapy (PRRT) but also for those who show progressive disease. PRRT not only reduces tumors but also prolongs survival. As opposed to chemotherapy (streptozocin- or temozolomide-based regimens) or to the newer angiogenesis inhibitors, such as sunitinib, PRRT clearly has less side effects. A routine QOL assessment - during and after treatment of NET - should allow for the development of preventive strategies and the establishment of well-defined medical and psychosocial interventions.

Differentiated TCA (DTC) generally has a favorable outcome. Still, thyroid disease, treatments, and morbidity can compromise health-related QOL. The standard care after surgery includes total thyroidectomy, ablation therapy with radioiodine and life-long thyroxine substitution therapy. TCA survivors generally are thought to have a similar or slightly worse QOL compared with the normative population. TCA patients may report some specific medical problems after cancer treatment and follow-up tests, which have a direct negative impact on medical problems after cancer treatment and follow-up tests, which have a direct negative impact on medical problems after cancer treatment and follow-up tests, which have a direct negative impact on medical problems after cancer treatment and follow-up tests, which have a direct negative impact on medical problems after cancer treatment and follow-up tests, which have a direct negative impact on medical problems after cancer treatment and follow-up tests, which have a direct negative impact on medical problems after cancer treatment and follow-up tests, which have a direct negative impact on medical problems after cancer treatment and follow-up tests, which have a direct negative impact on medical problems after cancer treatment and follow-up tests, which have a direct negative impact on medical problems after cancer treatment and follow-up tests, which have a direct negative impact on medical problems after cancer treatment and follow-up tests, which have a direct negative impact on medical problems after cancer treatment and follow-up tests, which
that QOL of TCA patients is reduced during the
time of thyroid ablation therapy until aftercare. To
alleviate symptom burden the need for medical or
psychosocial intervention needs to be identified
timely. The assessment of baseline QOL could be the
basis to adapt the treatment protocols, the preventive
strategies, and medical information to patients for
potentially improving outcomes.

O-073

Quality of Life in Oncological Patients
and Radionuclide Therapy

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Neuroendocrine tumors - what we now describe as
‘NET cancer’ - is a relatively rare disease which is
poorly understood and is often misdiagnosed. As
recently as 25 years ago, there was no medication
and no treatment available other than surgery. But
this has changed dramatically with the discovery
that neuroendocrine tumors frequently express a
high density of receptors which bind somatostatin
and various synthetic peptides. This has led swiftly
to the evolution of precise imaging techniques
and therapy using targeted radiation. From the
patients’ perspective, a diagnosis of NET cancer is
no longer a terminal illness. Today one can view
NET cancer as a chronic disease if it is well-managed
using a combination of surgical debulking, regular
monitoring with receptor-based imaging techniques
and properly-staged peptide receptor radiotherapy.
The patient journey is ideally one in which they work
collaboratively with their specialist physicians to
diagnose and treat the disease. The guidance which
patients need as they embark on this journey is to
seek coordinated multidisciplinary care, ideally from
a centre of excellence, and ensure that their treatment
follows consensus guidelines. Such patients can live
long productive lives.

O-074

THERANOSTICS: From Molecular Imaging Using PET/CT with Ga-68 Labelled Tracers to Personalized Therapy

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The acronym THERANOSTICS characterizes the
emerging field of molecular targeting of vectors which
can be used for both, therapy and diagnosis, when
modified accordingly. This term was specifically used in
the context of certain radiopharmaceuticals, so that the
same pharmaceutical (e.g., a peptide) when labeled with
a positron emitter, can be used for diagnosis using PET/
CT, and when labeled with a beta emitter, may be used
for therapy of a particular disease, targeted specifically
by that radiopharmaceutical. The importance of
THERANOSTICS is that it takes into account personalized
management of disease. THERANOSTICS embodies
both molecular and personalized medicine. Molecular
phenotypes in neoplasms can be determined by molecular
imaging using PET and SPECT with specific probes, so
that the treatment is specifically targeted against the tumor
and its environment. To meet these demands, we need to
define the targets, ligands, coupling / labeling chemistry,
radiouclides, biodistribution modifiers and finally to
choose the right patients for personalized treatment.\[1-4\]

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