

DIVISION OF SURGICAL ONCOLOGY

IMAGE GUIDED SURGERY

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This research line, which has started recently, is aiming at optimizing surgical procedures by better surgical guidance during operative procedures. To this end new imaging technologies are developed and tested to improve tumor mapping and staging pre and intra-operative. These imaging and surgical guidance procedures should lead to more radical resections while sparing normal tissue and organ function. The research line is a strong collaboration between the NKI-AVL, Technical University Twente and industrial partners. For the moment three projects are running. In the first project we are developing a tool for optical biopsies by means of spectroscopy and fluorescence techniques. An optical needle was developed together with industry. Ex vivo tissue specimens from more than hundred patients have been analyzed with an accuracy of over 90%. In vivo testing is planned early in 2011. In a second project, in cooperation with the group Biomedical Physics and Biomedical Photonics of AMC, optical coherence tomography is tested for improved tissue diagnosis in vulvar neoplasia, penis cancer and skin malignancies. A third project concentrates on the use of photoacoustic imaging for diagnosis of lymph node metastases and is running in close collaboration with the Biomedical Photonic Imaging group of the University of Twente. We recently showed that photoacoustic imaging is able to detect microscopic tumor foci within lymph nodes of melanoma patients. The research performed in these projects should lead to strong synergy with the new innovative minimal invasive operating theatre complex planned to be build in 2013 and should result in a technology platform that can be used for further clinical studies.

GYNAECOLOGY

Gemma Kenter, Marc van Beurden, Willemien van Driel, Petra Biewenga, Jan Lange, Lotti Lubsen-Brandsma, Monique Brood, Pia Kvistborg

The department focuses on innovative treatment for ovarian cancer, on interventions to improve quality of life for premature (iatrogenic) menopausal symptoms and for cervical carcinoma and immunotherapy for HPV related (pre)malignant genital neoplasms. Research takes place in close cooperation with the other centers from the Center for Gynaecologic Oncology Amsterdam (CGOA).

Ovary In a randomized multicenter phase III clinical trial for stage III ovarian carcinoma coordinated by the NKI-AVL the effect of secondary debulking surgery with or without hyperthermic intraperitoneal cisplatinum is being studied. Inclusion started march 2007 and currently runs in 5 centers in The Netherlands. It is expected that 4 additional centers in Belgium and France will participate. During interval debulking patients are randomized between interval debulking alone or in combination with infusion of cisplatinum under intra-operative hyperthermic condition. Primary endpoint of this study is progression free survival (KWF CKTO2006-16).

In a multicenter trial the effect of different hormonal replacement regimen on bone density, breast density and quality of life after prophylactic bilateral salpingo oophorectomy are examined in a randomized control trial (M05HIR Hirise). The effect of hormonal replacement therapy on menopausal complaints related to biochemical changes in surgically and naturally postmenopausal women is investigated in a prospective observational comparative study (M06HRT Novaria). A multicenter randomized trial to investigate the effect of cognitive behavioral therapy (CBT) and physical exercise for climacteric symptoms in breast cancer



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patients experiencing treatment-induced menopause is finalized, the results of which are analyzed (KWF 2006-3470).

The beneficial effect of a laparoscopy in order to predict the operability in high stage ovarian carcinoma will be studied in a multicenter randomized trial coordinated by the CGOA (ZON MW doelmatigheid 80-82310-97-11056).

Vulva Participation in the GROINSS-V II study, an international multicenter observational study on patients with vulvar cancer. Patients with positive lymph nodes, diagnosed by sentinel node technic, undergo radiation without full lymphadenectomy. Endpoints of this study are recurrence free survival and quality of life. For patients with locally advanced carcinoma of the vulva an efficacy study is ongoing during which patients are treated with induction chemoradiation and if necessary followed by surgery in order to reduce postoperative morbidity (AMC locally advanced vulvar cancer efficacy study).

The benefit of wearing therapeutic elastic stockings in order to prevent lymphedema for patients treated with inguinal lymph node dissection is conducted in a non-blinded, randomized controlled trial (Mo6PRO Kousen study). Inclusion was finalized and results will be available in 2010.

Optical coherence tomography (OCT) is an emerging biomedical optical imaging technique that performs high resolution, cross sectional tomographic imaging generating pictures that resemble histopathological examination. We will investigate the potential role of OCT as "optical biopsy" device in patients with (pre)malignant vulvar disease.

We reported on the clinical efficacy in 58% of imiquimod for treatment of usual type vulvar intraepithelial neoplasia (uVIN). We have assessed numbers of immunocompetent cells, expression of p16INK4a in relation to HPV clearance in relation to clinical response. Data indicate that imiquimod-induced clearance of HPV, is confirmed by normalization of p16INK4a expression and in normalization of immunocompetent cells in the dermis which is strongly correlated to histologic regression.

Patients with VIN III take part in a multicenter randomized trial to study the effect of vaccination with synthetic long HPV 16 E6/E7 peptides with or without imiquimod on the vaccination site.

Cervix A multicenter trial has recently been approved by the CCMO to study the efficacy of combined chemo-immunotherapy in high stage or recurrent carcinoma of the cervix.

A multicenter trial has been prepared to study the efficacy of combined chemo-immunotherapy. Furthermore, preparations for a phase I trial with DNA HPV 16 E7 vaccination in patients with HPV related disorders of the genital region or head and neck region are being made.

BREAST CANCER

Emiel Rutgers, Hester Oldenburg, Marie-Jeanne Vrancken Peeters, Jos van der Hage, Mila Donker, Stella Mook, Tjeerd Aukema.

Adjuvant! Online (www.adjuvantonline.com) calculates a 10-year survival probability based on the patient's age, tumor size, grade and estrogen receptor. To investigate whether the predictions by Adjuvant! are applicable to the Dutch breast cancer population, we conducted a retrospective validation study in 5380 patients. Our results show that Adjuvant! predicts both prognosis and treatment benefit accurately in the whole group and in most subgroups, with an overestimation in patients under 40 years of age with an ER+ tumor.

Mammographic screening has led to a proportional shift towards earlier stage breast cancers at presentation. The aim of our study was to assess whether method of detection provides prognostic information beyond standard prognostic factors. In our study cohort of 2592 invasive breast cancer patients screen-detection was an independent prognostic factor for reduced all-cause- and breast cancer-specific mortality, compared to non-screening-related carcinomas. Therefore, method of detection should be taken into account when estimating individual prognosis.

We assessed the influence of neoadjuvant chemotherapy for invasive breast cancer on short-term complications after skin sparing mastectomy and immediate prosthetic reconstruction. Therefore the surgical outcome in patients treated with neoadjuvant chemotherapy was compared to patients without preoperative chemotherapy. Since the overall complication rate was similar, we concluded that neoadjuvant chemotherapy does not increase the rate of immediate postoperative complications after skin sparing mastectomy and immediate reconstruction. We developed a new surgical technique to evaluate the axillary nodal response by Marking of the Axillary lymph node with Radioactive Iodine (MARI) seeds prior to neoadjuvant chemotherapy and selectively remove them after the neoadjuvant chemotherapy. Since the identification rate of the MARI node was high (95%) and the MARI node gave an accurate indication for the response in the additional nodes in 95%, we concluded that this procedure is feasible and promising for selecting patients for a more conservative axillary treatment after neoadjuvant chemotherapy. In cooperation with the PSOE we performed a RCT (EVA) evaluating the effectiveness of cognitive behavioural therapy, physical exercises and the combination of both interventions on premature menopause in breast cancer patients. First analysis of the final results show significant effect sizes for e.g. menopausal symptoms and hot flushes. We are preparing an RCT (POWER) to study the axillary recurrence rate in primary operable breast cancer patients that have a positive sentinel node and do not undergo completion locoregional axillary treatment.

GASTRO-INTESTINAL CANCER

Vic Verwaal, Theo Ruers, Johanna van Sandick, Frits van Coevorden, Marie-Jeanne Vrancken Peeters, Arend Aalbers, Ewout Courrech Staal, Martine Bloemer, Karen Bloemendal, Maurits Swellengrebel, Sjoerd Bruin, Danny Evers, Loes Velthuisen, Jarich Spliethoff

Oesophagus Several studies were performed to investigate whether biological markers can improve individual treatment planning in patients with non-metastatic oesophageal cancer. The tumour-stroma ratio was examined on archival biopsy material and proved to be an independent prognostic factor for survival. In an other study, the incidence of mutations in *EGFR*, *KRAS* and *BRAF* was studied in oesophageal cancer biopsies from patients who were treated with chemoradiotherapy and surgery. In none of the 30 patients, mutations were found. Therefore, prudence is warranted when introducing targeted therapies on the basis of *EGFR*, *KRAS* and *BRAF* mutations in the treatment of oesophageal cancer.

We reviewed the literature on quality aspects of oesophageal cancer surgery. There was strong evidence that both hospital and surgeon volume are important determinants of postoperative mortality. The most commonly reported process measures were determinants of patient selection for surgery. The level of evidence for pathological outcome measures was high. This review indicated that there is a need for uniformity in the evaluation of quality of care. A study was undertaken to investigate the quality of care for 821 oesophageal cancer patients who were seen at the NKI-AVL between 2003 and 2008. By evaluating different dimensions of healthcare quality, we have identified which steps in the multidisciplinary care path need more attention in order to raise the whole level of care.

Hipec The most eye catching study performed by the HIPEC group is a study in which a new classification of peritoneal metastases is made based on cell atypia, mitosis index and percentage of mucous on one side and survival on the other side. PM could be categorized into four groups: low-grade, well-differentiated mucinous tumor (DPAM); intermediated-grade mucinous carcinoma (PMCA-i); high-grade mucinous carcinoma (PMCA); and high-grade nonmucinous carcinoma (PCA). Multivariate analysis showed that histological classification, gender, number of segments affected, completeness of cytoreduction, and HIPEC as primary treatment were significant related to OS and DFS. The 5-year OS was 64% in the DPAM group, 36% in the PMCA group, and 24% in the PCA group. Of PM originating from an appendix tumor, 29% were of non-DPAM type. Of primary colorectal tumors, 37% resulted in mucinous PM, and another 26% of PM of colorectal origin had partly

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Publications

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mucinous histology. The conclusion of this study was that histology is a significant predictive factor of OS and DFS in PM treated with surgical cytoreduction and HIPEC. Due to collaboration between the HIPEC centres in the Netherlands a large epidemiologic study (3356 patients) is performed on the change in survival of metastasized colon cancer over the last decades. This study showed that the median survival of patients with liver metastasis changed from 34 (1995 – 2000) to 51 weeks (2001 – 2006) where as the survival of patient with PM stayed the same (35 in 1995 – 2000 and 30 weeks in 2001 – 2006). A second finding was that the most patients with peritoneal carcinomatosis were still treated with systemic chemotherapy only, instead of with HIPEC.

Colorectal liver metastases Research is focused on imaging and local tumour destruction. The results of an international randomized study on the use of RFA for unresectable colorectal liver metastases were presented as an oral at ASCO 2010. Further research is directed at immunological cell death and immunostimulation after local tumour destruction (e.a. HIFU) within a CTMM consortium. Together with the Technical University Twente gold nanoshells, in combination with NIR light, are used for tumour detection and ablation of resection margins. In collaboration with industrial partners the use spectroscopy for tumor diagnosis and guidance of minimal invasive procedures is investigated. The research line is funded by KWF, the UTwente, EORTC and industrial partners.

MELANOMA

Jos van der Hage, Bin Kroon, Omgo Nieweg, Martijn Stuijver, Hidde Veenstra, Ronnie Wessels, Michel Wouters

The research activities of the melanomologists concern the anatomy and physiology of the lymphatic system, implications for dissemination, implementation of new forms of imaging techniques and other new forms of diagnostic and staging methods, sentinel node biopsy, aspects of inguinal node dissection, in transit metastases and aspects of regional isolation perfusion.

Eight years ago, we found a 23% incidence of in transit metastases in patients with an involved sentinel node. This high percentage was reason for concern. Now, in our much larger patient population, we found no predisposition for in-transit metastases and we consider this issue resolved definitively.

Melanoma surgeons are struggling with the question whether every patient with a tumour-positive sentinel node needs a completion node dissection. Of interest, **patients with a subcapsular metastasis smaller than 0.1 mm have a 91% five-year overall survival rate and a 9% incidence of involvement of other lymph nodes.**

One may consider sparing these patients a completion node dissection. Lymph node dissections, especially in the groin are associated with substantial morbidity. Identifying the patients at risk for major wound complications (i.e. dehiscence) pre-operatively could influence operative techniques and peri-operative care. In a retrospective study of 236 groin dissections these risk factors were identified and peri-operative measures to decrease morbidity in these patients, like minimal invasive operative techniques, are now under consideration.

There is one prospective randomized trial looking at whether lymphatic mapping improves survival. A recent interim analysis of this RCT (led by Dr. D.L. Morton) confirmed that the mean number involved nodes in patients with an involved sentinel node is 1.4, yet this number increases to 3.2 by the time lymph nodes become palpable (p=0.0001). Melanoma specific survival is significantly better in the patients with a tumor-positive sentinel node: 61% versus 42% in the patients who were initially observed and who came back with palpable lymph nodes later on during follow up (p-value 0.01).

Several locoregional treatment options for advanced melanoma patients exist. Different treatment modalities range from local excision to isolated limb perfusion. Although isolated limb perfusion is a very effective therapy, it is a highly complex procedure. Another modality is CO₂ laser therapy. CO₂ laser therapy is a simple and effective therapy applicable to patients with multiple in transit metastases without significant morbidity. In 2010, patients who underwent this type of therapy

in the past 4 years in the Netherlands Cancer Institute were analyzed. CO₂ laser was demonstrated to be a safe and effective treatment modality associated with an almost 100% limb salvage rate.

LIPOSARCOMA STUDY GROUP

Frits van Coevorden, Daphne de Jong, Petra Nederlof, Rick Haas,
Harm van Tinteren, Ronald de Vreeze

We analyzed our liposarcoma database of 325 patients (1977-2007) and subjected the material to additional tests for improved classification and grading. Adding clinical information of these cases created a set of data for further study and analysis. The occurrence of combined patterns of well-differentiated liposarcoma (WDLS) and myxoid/roundcell liposarcoma (MRLS) designated as mixed-type liposarcoma pose a conceptual problem as this feature may have consequences for treatment choice and prognosis. We have dissected the molecular relation of tumor components in cases of mixed-type liposarcoma. Based on heterogeneous preoperative MRI features, 8 cases were selected. Preoperative biopsies and resection specimens were analyzed including molecular and immunohistochemical analysis on all components. As controls, cases with homogeneous MRI features and uniform aspects of 10 MRLS and 5 WDLS were studied. All patients with heterogeneous MRI features showed morphological components of MRLS and WDLS. RTPCR showed FUS-DDIT3 fusion in both components in 5/8 cases in the absence (0/5) of MDM2 and CDK4 amplification. In 3/8 patients, MDM2 and/or CDK4 were overexpressed, and amplification was shown by MLPA in the absence of MRLS translocations. All control patients showed a molecular pattern consistent with their morphological features. Therefore, mixed-type liposarcomas should not be regarded as collision tumors, but as an extreme variant of the morphological spectrum within a single biological entity, explaining the biological contradiction of mixed-type liposarcoma. For treatment stratification, detailed classification including molecular support should be performed in tumors with heterogeneous MRI features.

The classification of multifocal myxoid/round cell liposarcoma (MRLS), which is defined as tumor presentation in at least two separate sites before manifestation in the lungs, as either metastasis or as a second primary tumor, has essential clinical consequences. MRLS is characterized by t(12;16)(q13;p11) or t(12;22)(q13;q12), and various exon fusion transcripts are described with varying incidences, which permits their use as markers for clonality. Moreover, in solid tumors, analysis of loss of heterozygosity (LOH) is valuable for clonality analysis. Therefore, fifteen multifocal MRLS-patients with 2-5 metachronous (n=12) or synchronous (n=3) localizations were investigated. Using RT-PCR, the detailed molecular characteristics of the FUS-CHOP and EWS-CHOP breakpoints were determined. LOH-analysis at twelve loci was then used to further analyze clonal relationships. In all patients, tumor sites showed identical FUS-CHOP fusion products. In six patients, identical rare fusion transcripts were found, supporting a clonal relationship. Nine patients had the common exon5-FUS/exon2-CHOP fusion transcript, and two of these were identified as clonally related by LOH-analysis. In all other patients, LOH-analysis was highly suggestive of a clonal relationship, and no evidence for interpretation of a second primary tumor was found. This study supports the metastatic nature of apparent multifocal myxoid/round cell liposarcoma.

THORACIC CANCER SURGERY

Houke Klomp, Michel Wouters, Johanna van Sandick, Erik von Meyenfeldt,
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Molecular imaging may play a critical role in the evaluation and treatment planning for NSCLC. The Mo6NEL study investigated the role of 18F-FDG PET/CT for the early identification of response to therapy in patients who were treated with a molecular-targeted agent (EGFR-TKI erlotinib). 18F-FDG PET/CT was used to monitor the disease before and at one week after administration of EGFR-TKI. Changes in tumor 18F-FDG uptake during treatment were measured by

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standardized uptake values. The results of the study suggest that early during the course of therapy, 18F-FDG PET/CT can predict response to treatment in patients with NSCLC. In locally advanced stage IIIA-N2 NSCLC, evaluation of induction chemotherapy followed by either surgical resection or radiotherapy, showed that outcome was favourable after lobectomy, but not after pneumonectomy (5-yr survival 43% versus 16%, 5-yr survival after radiotherapy 16%). Newer induction protocols combining (daily low-dose) chemotherapy with high-dose radiation (66 Gy) are ongoing as the M07CCL (Raditux) study using cetuximab in combination with concurrent chemoradiotherapy. A collaborative study will investigate the role of surgery following such intensified chemoradiation protocols.

Our department participated in the EORTC 08031 phase II trial investigating the feasibility of trimodality therapy that consisted of induction chemotherapy followed by extrapleural pneumonectomy and postoperative radiotherapy in patients with malignant pleural mesothelioma. Although feasible, trimodality therapy in patients with mesothelioma was not completed within the strictly defined timelines of this protocol and adjustments are necessary.

Local treatment of pulmonary metastases is considered in patients with (oligo) metastatic disease, in whom primary tumour control has been achieved. The role of local treatment by either thoracotomy, video-assisted thoracoscopic procedures and local ablation techniques for long-term disease control in oligometastatic disease has been evaluated (for several primary tumor types).

Variation in quality of care provided by different institutions is the subject of an intensive debate in the Netherlands. A study of the Quality of Cancer Care taskforce of the Dutch Cancer Society showed that outcome of bladder, colorectal, breast and lung cancer patients in the Netherlands varies by region and the hospital their cancer was diagnosed in. However, hospital characteristics like a high diagnostic volume, teaching status or availability of radiotherapy facilities proved no guarantee for optimal treatment rates.

HEAD AND NECK SURGERY AND ONCOLOGY

Alfons Balm, Michiel van den Brekel, Frans Hilgers, Martin Klop, Peter Lohuis, Ludi Smeele, Bing Tan, Baris Karakullukcu, Charlotte Zuur

The department of head and neck surgery and oncology is a national referral centre and one of the larger clinical departments in this field treating about 600 new patients annually. The department is active in clinical and translational research. Currently, 3 full professors are part of the department and staff has part-time positions in the Academic Medical Centre (AMC) of the University of Amsterdam. Being a multidisciplinary field, there are many clinical and research connections within the institute and also in the AMC.

Translational Research In 2010 the head and neck department was involved in several translational projects. Together with Adrian Begg and Conchita Vens we studied the Fanconi pathway in oral cancer samples as well as cell lines. In about 15% of cell lines there is a phenotype of Fanconi deficiency. Currently some 100 patient samples are sequenced. This finding opens the way to start looking for alternative treatment strategies such as PARP inhibitors. In a project together with Marcel Verheij on the BCL2 inhibitor gossypol, a clinical phase two study has been started in patients treated with cisplatin based chemoradiation. Together with Jacques Neeffjes and the department of pulmonology we have set up a protocol for short term cultures. These can be used to test chemosensitivity pretreatment and also be used to test the chemical library of Huib Ova to look for new targets. In cooperation with the NWHHT (Dutch Cooperative Head and Neck Group) genetic markers predicting progression from dysplasia to cancer are studied. This year an expression profile predicting lymph node metastases as developed by Roepman et al, has been validated in a large Dutch patient cohort. Early detection and monitoring treatment outcome of nasopharyngeal cancer using (anti-)Epstein-Barr Virus (EBV) based tumor markers is studied in the Netherlands, UI-Jakarta, UGM-Yogyakarta together with the VUmc. With the same group a project on lymfatic induction therapy in recurrent nasopharyngeal cancer has been approved by the KWF.

Photodynamic Therapy The department is active in research on photodynamic therapy and several grants have been obtained (VENI, ZonMW, NWO, KWF). Currently the focus of this research is on interstitial PDT. In several projects treatment planning and dosimetry for interstitial PDT is studied by means of developing pretreatment planning tools and intraoperative imaging guidance. In a national study with participation of all academic medical centers in the Netherlands, the cost effectiveness of Foscan PDT for incurable recurrent head and neck cancers is being studied. Monitoring of tissue oxygen saturation and Foscan concentration during PDT to optimize treatment parameters is another project.

Rehabilitation Rehabilitation research focuses on several topics. Prevention of trismus, swallowing and speech problems in patients treated with chemotherapy for advanced head and neck cancer is one field of research. An evidence based rehabilitation program has been set up in 2010. In a project on pulmonary rehabilitation after laryngectomy, in cooperation with ATOS, new heat-and-moist-exchangers are being developed and tested using an artificial airway system, but also in patients. Mucociliary transport in the trachea after laryngectomy is another field of interest. Together with the university of Amsterdam centre for language and communication (ACLIC), an automatic speech analyzer has been developed for pathologic voices, such as after laryngectomy or chemoradiation. A project to use these systems in rehabilitation was started.

Clinical Research Clinical research is quite diverse. Fields of interest are sentinel node detection, imaging, prediction of inoperability clinical trials using novel chemotherapy regimens and clinical and biological aspects of young patients with head and neck cancer. The use of SPECT-CT and intraoperative imaging using both the Sentinella and fluorescence is assessed and has been found useful in oral cancer and melanoma. Studies on modelling tumor resection and functional outcome prediction are done in cooperation with the Technical University Twente and VUmc.

UROLOGIC ONCOLOGY

Simon Horenblas, Axel Bex, Wim Meinhardt, Henk van de Poel,
Richard Meijer, Chantal Nunnink, Niels Graafland

Research in urologic oncology has been centred around the following themes: Improved staging of urologic tumours, organ and function sparing, fundamental research in prostate, kidney and penis cancer.

Improved staging of urologic tumours Research has been focussed on the role of sentinel node biopsy in kidney, prostate, testicular and penile cancer. In all above mentioned tumours, apart from kidney cancer, sentinel node biopsy has proven to be extremely useful in minimizing the morbidity of surgery of the lymph nodes and at the same time maximizing the detection rate of occult lymph node metastases. The collaboration with the department of nuclear physics has been very fruitful. Especially the use of SPECT /CT scans and intra-operative imaging with a mobile gamma camera (Sentinella®) has proven to be a clinical useful adjunct. In prostate cancer no false negative findings were observed. The sentinel node strategy together with the Sentinella was effective in localizing sentinel nodes in a variety of anatomical locations, otherwise not removed during lymph node dissection. The scope of research has been widened by collaboration with the department of clinical physics. A comparative trial was started, comparing patent blue, ICG and ICG with technetium. Using a fluorescence camera ICG is seen after i.v. injection. In testicular cancer also no false negative findings have been observed. Accrual in this clinical study is very slow unfortunately, mainly because of the fact that stage I germ cell tumours are mostly been treated outside of NKI-AVL. In penile cancer the false negative rate dropped from 20% to an acceptable 5.1%. For renal cancer we continue with the sentinel node study, approved in 2008, with the aim of elucidating the lymphatic pathways of renal cancer and the immunological effect of renal cancer in the sentinel nodes.

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Organ and function sparing The role of cytoreductive surgery in metastatic renal cancer is further being investigated in a randomized EORTC study comparing immediate versus deferred nephrectomy for patients with synchronous metastatic renal cell carcinoma and the primary tumour in situ. This study (E 30073) coordinated by Axel Bex, followed the experiences of the phase II study with neo-adjuvant Sutent (tyrosine kinase inhibitor).

In bladder cancer we continue to expand our experiences with the so called Sexuality Preserving Cystectomy and Neobladder (SPCN). In a recent publication excellent continence and potency rates were seen without any danger of increased recurrences. Despite international scepticism we continue to advocate this procedure in well selected patients. In line with the wish to decrease the morbidity of the surgery robotic assisted cystectomy was started in 2010.

Improving early urine continence after robot assisted laparoscopic prostatectomy (RALP) led to a randomized study on the role of ventral suspension using the vas deference. A previous randomized study was completed showing no benefit for reconstruction of the median fibrous raphe in men after RALP.

We are involved in the active surveillance study for prostate cancer (Prias, initiated by Rotterdam) and have entered more patients than any one else.

We are partners together with Rotterdam and Groningen in the PCMM consortium regarding prostate cancer and prostatectomy

TRANSLATIONAL RESEARCH IN PROSTATE, KIDNEY AND PENILE CANCER

Prostate cancer The role of Pim-1 expression in prostate cancer progression is investigated. Pim-1 was earlier shown to enhance the growth response of prostate cancer cells in vitro to low levels of DHT. A possible explanation for this may be the downregulation by Pim-1 of the 17-beta-hydroxysteroid-dehydrogenase type 2 gene product (HSD17B2). HSD17B2 is involved in the enzymatic down regulation of DHT and testosterone in breast and prostate cancers. Its down regulation by Pim-1 overexpression may aid prostate cancer cells to survive in low testosterone environments, such as in castrate resistant prostate cancer (CRPC).

The role of mTOR inhibition in chemotherapy is being assessed in a phase I study in collaboration with Andre Bergman, medical oncologist. In this study the combined use of everolimus (mTOR inhibitor) and cyclophosphamide in CRPC will be tested. In collaboration with Prof. Ton Schumacher the role of T-cell receptors in prostate cancer model vaccination studies was addressed.

Penis cancer The role of HPV in penis cancer was further investigated in close collaboration with the department of pathology of the Free University medical centre. Using molecular and serological analyses for a wide range of HPV types and comparing serological findings with age-matched male controls. Primarily HPV 16 infection is directly involved in penile carcinogenesis. Based on earlier micro-array results a renewed analysis was started comparing HPV+ and HPV- tumors.

Kidney cancer In collaboration with the department of immunology, the department of angiogenesis of Arjan Griffioen at the Free University medical centre and Eric Jonasch, MD Anderson Cancer Center, Houston, kidney cancer tissue is analysed, specifically looking into neo-vascularization and immune modulation. Also together with the department of immunology analysis of rapid expansion of TIL cells was started.

Improved quality control of treatment results Using prospective data collection, almost all uro-surgical treatments at the NKI-AVL can be analysed now. Extensive use of these databases was made for prostate, bladder and penile cancer. Quality of life analysis was done of in patients with localized prostate cancer managed by brachytherapy or robot assisted laparoscopic prostatectomy (RALP). Prospective data are analysed for risk estimation of treatment or active surveillance for prostate cancer within the framework of the IMPACT-study, funded by ZonMW. Together with the Comprehensive Cancer Center Amsterdam a comparative study was published looking at recurrences in bladder cancer as a quality control tool. Treatment related parameters were analysed in low volume and high volume

hospitals and compared with the results in the NKI-AVL. Although the recurrence rate did not differ between the NKI-AVL (high volume hospital) and the other hospitals, the early post-operative death was less than in other hospitals (0.6% versus 4.3%).

ANESTHESIOLOGY AND INTENSIVE CARE MEDICINE

Peter Schutte, Dirk Buitelaar, Katina Efthymiou, Christoph Hahn, Sandra Huissoon, Lenie Hulshoff, Michael Šrámek, Julia ten Cate, Ingeborg Vergouwe

The principal aim of the Department of Anesthesiology and Intensive Care Medicine is to deliver the highest standard of anesthesiological and intensive care.

Presently our research focuses mainly on the role of peripheral nerve and central neuraxial blockades as an adjuvant to general anesthesia. The purpose of these blockades is threefold: a reduction in perioperative opioid consumption, the prevention of chronic pain and shortening of length of hospital stay.

In collaboration with the Departments of Surgical Oncology, Head and Neck Oncology and Urological Oncology, innovations are/have been implemented. E.g. superficial cervical plexus blockade in patients undergoing head and neck surgery, field blockade and paravertebral blockade in breast surgery and transversus abdominis plane blockade (TAP-block) in, for instance, robot assisted laparoscopic prostatectomies.

The results of the No7TAP-trial are evaluated and submitted for publication. Furthermore two more study protocols are currently being developed. One study focuses on perioperative pain treatment in patients undergoing laryngectomies and commando resections. In this study the beneficial effects of intravenous S(+)-Ketanest and lidocaine will be studied. The other study focuses on the intraoperative position of patients undergoing thoracotomies in relation to the prevention of postoperative ipsilateral postthoracotomy shoulder pain.

Future focus of interest is the role of regional and general anesthesia in the prognosis of surgically treated oncologic patients.

PLASTIC AND RECONSTRUCTIVE SURGERY

Marieke van den Berg, Brigitte Drost, J Joris Hage, Martine van Huizum, Arjen van Turnhout, Carolien Wever, Leonie Woerdeman

The research of the Department of Plastic and Reconstructive Surgery is focused predominantly on innovative reconstructive techniques after ablative surgery by other specialists. Additionally, ongoing vascular and functional research was done in collaboration with the Department of Plastic Surgery at the University Medical Centre Utrecht (prof. dr. M. Kon).

Vascular anatomy and clinical application of internal mammary artery

perforator flaps Internal mammary artery perforator (IMAP) pedicled or free flaps allow for superior skin cover of regional oncological defects and primary closure of the parasternal donor site associated with limited associated donor site morbidity. In collaboration with the UMCU, the dominant and non-dominant perforators and their vascular territories were objectified. Mobilization of the vascular pedicle resulted in an increase of its length of 4.7 cm and, consequently, to double that increase of the arc of rotation of the pedicled IMAP flap. The clinical reliability of the IMAP free flap was proven.

Immediate prosthetic breast reconstruction after neoadjuvant chemotherapy

Neoadjuvant chemotherapy is gaining acceptance as an option for breast cancer treatment but it is not known whether preoperative chemotherapy hampers wound healing after skin sparing mastectomy and immediate prosthetic breast reconstruction. The outcome of such combined surgery in women treated with neoadjuvant chemotherapy from 2006 through 2009 was compared to that in women without preoperative chemotherapy. The overall rate of postoperative complications was less among neoadjuvantly treated women than in the control

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group (0.15 vs. 0.29; $p = 0.042$) and resulted in less loss of prostheses (0.08 vs. 0.11; $p = 0.566$). Immediate prosthetic reconstruction is an attractive treatment option for this particular group of patients also.

Reconstruction of oncological perineo-vulvar defects: An algorithm of sequence

Because both VIN and vulvar carcinoma have a tendency towards local recurrence, future reconstructive options should be reckoned with during treatment of the primary and all subsequent perineo-vulvar lesions. A proposal of sequence of reconstructive options for these defects was called for.

Local skin flaps are preferably designed so as not to sever the branches of the internal pudendal vascular system. Initial use of the pudendal thigh flap is preferred over the infragluteal flap to preserve the infragluteal flap for future use. Only when these two flaps no longer are sufficient should the gluteal thigh flap be applied. Myocutaneous flaps are rarely indicated.

DERMATOLOGY

Esther Tjin, Debbie Konijnenberg, Gabrielle Krebbers, Henk Mallo, Jan Wouter Drijfhout, Kees Franken, Chantal van der Horst, Jan Bos, Omgo Nieweg, Bin Kroon, John Haanen, Kees Melief, Florry Vyth-Dreese, Rosalie Luiten

Integrated analyses of melanoma – T cell interactions: relevance for immunotherapy

Clinical studies have shown that immunotherapy of melanoma by vaccination or adoptive transfer of effector T-cells can mediate tumor regression. However, a significant number of melanoma patients either respond poorly or show relapse. This might be either caused by tumor resistance to T-cell-mediated lysis or impaired effector T-cell function. We analyzed the presence of melanoma antigen-specific T cells in the melanoma tissue, as compared to T cells in the adjacent skin tissue and in the peripheral blood. More specific T cells were found in the tumor than in the adjacent skin or blood. Interestingly, functional T cell analysis revealed 2 groups of patients: 1) patients with functional CD8+ T cell responses and 2) patients with non-functional CD8+ T cell responses. More importantly, although no correlation was found between the T cell effector function and patients' survival, patients with non-functional T cell responses showed loss of HLA expression in the melanoma more frequently, whereas the other escape mechanisms did not differ between the groups. These findings have major implications for selecting therapeutic strategies to treat melanoma patients, in particular, which patients may benefit from immunotherapy.

Hansje-Eva Teulings, Esther Tjin, Ludmilla Nieuweboer-Krobotova, Jos van der Hage, Michel Wouters, Wietze van der Veen, Jan Bos, Kees Melief, John Haanen and Rosalie Luiten

Local immunotherapy by the synergism of monobenzone and imiquimod cream (MI) for cutaneous metastases in stage III-IV melanoma patients

Melanoma is a good candidate for treatment with immunotherapy, during which vitiligo development is a favourable prognostic sign. At the department of Dermatology of the AMC, we have developed a new therapy for melanoma, based on the potent vitiligo-inducing effect of monobenzone combined with the immunostimulatory adjuvant imiquimod (MI therapy). MI therapy induces strong melanoma-reactive immunity, which effectively eradicated established melanoma in mice (van den Boorn et al, PLoS one 2010).

Based on these data, we will start a phase II clinical trial of monobenzone-imiquimod (MI) therapy in melanoma patients at the NKI-AVL in 2011. The MI regimen is a low-cost, simple therapy, which is applicable in broad range of patients regardless of HLA-haplotype. It does not require elaborate patient-specific in vitro cultures nor non-myeloablative lymphodepletion, reducing patient treatment burden. The MI compounds have each already been used in humans, making it readily available and easily applicable in the clinic. In this trial, we will investigate the local antitumor effect of MI therapy in melanoma patients as well as the induction of melanocyte/melanoma-specific immunity.

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