2rd International Conference on Innovative Approaches in Head and Neck Oncology

Meeting Report

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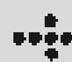
The second International Conference on Innovative Approaches in Head and Neck Oncology was attended by around 1000 delegates from 30 countries and 150 abstracts were submitted for the scientific part of the conference. The focus of this conference was on patient selection criteria; identifying patients who will benefit from specific treatments or are at risk of toxicity, quality assurance in the treatment of head and neck cancer patients, and the availability of evidence-based data in the treatment of these patients. During a 2.5-day program of keynote lectures, symposia, proffered paper sessions and case discussions, these topics were covered in a comprehensive and multidisciplinary manner.



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Patient selection in head and neck cancer

From the bench to the clinic

J. Grandis discussed the importance of the recent knowledge on signaling pathways in the management of patients with squamous cell cancer of the head and neck (SCCHN) and of the interaction between the clinic and the laboratory. Signaling pathways offer conditions for possible interference by medication since the target is often over-expressed; the expression levels of the target correlate with survival. Blocking the pathway has been shown to inhibit tumor growth in preclinical models. Based on these concepts she discussed clinical study designs that look at the signaling pathway and target in the patient. Patients are treated after biopsy with the agent of interest, evaluated by imaging, and the material for molecular studies is collected by surgical treatment.

She further discussed the role of the epidermal growth factor receptor (EGFR), which is over-expressed in up to 90% of head and neck tumors. Despite this over-expression only 10-15% of patients react to the EGFR-directed monoclonal antibody cetuximab. Potential mechanisms for lack of response to EGFR inhibition in SCCHN include constitutive activation of signaling pathways independent of EGFR, as well as genetic aberrations causing dys-regulation of the cell cycle. The activated receptor recruits signaling complexes and activates the ras–mitogen-activated protein kinase kinase (MEK)–extracellular signal-regulated kinase (ERK), phosphatidylinositol (PI) -3-kinase–akt, signal transducers and activators of transcription (STATs), and phospholipase C gamma (PLC-) pathways. These pathways are potent oncogenic regulators of tumor cell growth, invasion, angiogenesis, and metastasis. Other pathways that are of importance are the paracrine mechanisms of c-MET; the transcription factor STAT-3 and the SRC-kinase pathway. She demonstrated the possibility to interfere with many of these pathways with new techniques.

C. Chung explained the use of gene expression profiling in the treatment of head and neck cancer.
She discussed first the prognostic role of different molecular markers.

- Human papillomavirus (HPV) infection is detected in a subset of patients with head and neck cancer. HPV DNA is present in 15-35% of patients with SCCHN and they present a subclass with different biology and clinical behavior. HPV-related head and neck cancers have a 2-year progression-free survival of 86%, versus 53% in non-HPV-related head and neck cancer, and a 85% versus 45% disease-specific 5-year survival. Gene expression profiles of HPV+ and HPV- tumors showed that in HPV+ samples there is an over-expression of cell cycle regulators (p16(INK4A), p18, and CDC7) and transcription factors (TAF7L, RFC4, RPA2, and TFDP2). These differentially expressed genes may explain the unique pathways in HPV+ tumors that result in the different natural history and biological properties of these tumors.
- She also discussed the EGFR, another important molecular marker. Over-expression of EGFR and its ligand, transforming growth factor alpha (TGF-), was prevalent in patients with SCCHN and EGFR and TGF- mRNA was elevated in 92% and 87% of tumors, respectively. EGFR levels increase in advanced-stage tumors and in poorly differentiated tumors. In addition to EGFR, other ErbB family members are also over-expressed in SCCHN (ErbB2, 3% to 29%; ErbB3, 21%; ErbB4, 26%). Downstream effectors of EGFR such as ERK1/-2, akt, STAT3, and STAT5 are found to be activated in SCCHN and are associated with a higher proliferative index and advanced SCCHN tumor stages.

The combination of HPV-positivity and low EGFR expression translates to a good prognosis, while the absence of HPV and high EGFR expression translates to a poor prognosis.

G. D'Souza discussed the epidemiological data linking HPV to oral cancer. She showed that the relationship fulfills almost all Hill epidemiologic criteria for determining causality. These criteria state that to demonstrate a causal relationship there has to be an exposure to the virus in patients with oral cancer; (2) that exposure increases the risk for oral cancer; (3) there is a dose-response relationship, with greater exposure resulting in higher risk; (4) the increased risk is robust and observed with various study methods, in multiple populations, and persists after controlling for other factors; (5) there are scientifically plausible mechanisms; and (6) no explanation other than causality can account for the evidence.

- Gillison et al. examined 253 patients with SCCHN by molecular techniques and could show HPV-DNA in 62 (25%) of them (95% confidence interval [CI] 19-30%). High-risk, tumorigenic type HPV16 was identified in 90% of the HPV-positive tumors within the nuclei of cancer cells in pre-invasive, invasive, and lymph node disease.
- Several case-control studies have reported certain sexual behaviors to elevate the risk of oral cancer.
  - Risk factors among men include young age at first intercourse, number of sexual partners, and a history of genital warts.
  - Risk factors among women are a high number of sexual partners.
  - Furthermore, specific sexual behaviors have been more strongly associated with risk of an HPV-positive tumor, including a history of performing oral sex and oral-anal contact.
- Direct measures of HPV exposure and infection have also been associated with risk of oral cancers. Seropositivity to the HPV16 viral capsid protein confers a 2- to 3-fold increase in risk for SCCHN. In case-control studies, the presence of an oncogenic, oral HPV

infection has been associated with a 6-fold increase in the risk for oral cancer. In a recent study conducted in Sweden, oral infection by a high-risk HPV type was demonstrated to dramatically elevate odds for oropharyngeal cancer (odds ratio, 230; 95%CI 44-1.200), after adjustment for alcohol and tobacco. In a case-control study conducted in Norway, HPV16-seropositive individuals had a greater than 14-fold increase in risk of subsequent oropharyngeal cancer when compared with seronegative individuals.

- Although natural history studies have not been conducted, it is presumed that oral HPV infection precedes the development of HPV-positive SCCHN.
- The HPV-positive patient also appears to be distinct from the HPV-negative patient with regard to alcohol and tobacco exposure history; HPV-positive patients with SSCHN are more likely to be non-smokers and non-drinkers.
- High-risk HPV are etiologic agents for anogenital tract cancers.

She also showed that patients with HPV-related oral cancer have a better prognosis; even when they are detected in later stages, the overall survival is better compared to smoking-related head and neck cancer.

The problem in the clinical practice is that there is no easily accessible validated technique to detect HPV in clinical tissues.

Imaging techniques

Several imaging techniques were reviewed in patients with SCCHN.

- R. Hermans discussed the role of computed tomography (CT)-scan and magnetic resonance imaging (MRI) during the initial diagnostic evaluation of head and neck cancer and their place in treatment monitoring and follow up.
  - At diagnosis, nodal metastases have an adverse prognostic impact in patients with SCCHN. It is thus important to detect regional metastases in order to prognosticate the patient's disease and adapt treatment. CT-scan and MRI remain the primary imaging modalities for loco-regional staging of SCCHN to evaluate the primary tumor and to detect non-palpable lymph nodes. However, both modalities rely on size-related and morphological criteria to differentiate between benign and malignant lymph nodes, decreasing the sensitivity for detection of small metastases.
  - In patients with suspected recurrent disease after primary treatment, diagnosis of recurrence by CT-scan and MRI is hampered by a number of treatment-related tissue changes that become visible on CT and MRI. These include changes due to inflammation and vascular damage.

  To overcome these difficulties, diffusion-weighted MRI (DW-MRI) measures can be used to detect differences in tissue microstructure, based on the random displacement of water molecules. The differences in water mobility are quantified using the apparent diffusion coefficient (ADC), which has an inverse relationship to tissue cellularity. This technique enables the differentiation between tumoral tissue and normal or necrotic tissue. Therefore DW-MRI can be used in combination with conventional imaging for staging of lymph nodes in head and neck cancer, before and after treatment, and for detection of recurrent disease.

- W. Oyen discussed the role of positron emission tomography (PET) with fluorodeoxyglycose (FDG) in patients with SCCHN. While is it not an optimal method to evaluate the primary tumor, it can be used in the staging of regional and distant disease. A recent meta-analysis of 32 studies in 1,236 patients with head and neck cancer showed that the sensitivity of 18F-FDG PET was 79% (95%CI 72-85%) and the specificity 86% (95%CI 83-89%). For cN0 patients, sensitivity of 18F-FDG PET was only 50% (95%CI 37-63%), whereas specificity was 87% (95%CI 76-93%). Overall, the positive likelihood ratio was 5.84 (95%CI 4.59-7.42) and the negative likelihood ratio 0.24 (95%CI 0.17-0.33). This means that 18F-FDG PET does not detect disease in half of the patients with metastasis and cN0. In studies in which both 18F-FDG PET and conventional diagnostic tests were performed, sensitivity and specificity of 18F-FDG PET were 80% and 86%, respectively, and of conventional diagnostic tests 75% and 79%, respectively.

  Other indications of PET such as biological tumor characteristics, staging, or detection of recurrent disease are being examined.

M. Lonneux explained the possibility of applying molecular imaging techniques in patients with head and neck cancer. It is possible with the new nuclear imaging to get a snapshot of the biology of cancer cells *in vivo*. FDG-PET is based on the fact that the uptake of 18F-FDG is substantially increased in most types of cancer as compared to normal organs or tissues due to the over-expression of glucose transporters, especially GLUT-1, and glycolytic enzymes such as hexokinase II.

There have been studies to look at the possibility of using PET as a prognostic tool, to evaluate its predictive value in relation to response to treatment, to look at relapses, and to study hypoxia and proliferation.

- FDG-PET may be used as a prognostic tool in patients with head and neck cancer.
  - The standardized uptake value (SUV) was tested to predict the prognosis of patients with SCCHN. A retrospective review of the SUV of pretreatment FDG-PET scans of 60 patients with SCCHN who were treated with radiotherapy or chemoradiation

showed that the group with low SUV(< 9.0) had a significantly better 2-year disease-free survival. However, different studies are using different cut-offs making standardization very difficult and explaining the inconsistent results.
- FDG-PET may be used during the initial management plan in patients with head and neck cancer to provide additional staging information and influence treatment outcome. In several small studies, PET scans resulted in management changes in 33.8% of patients. Moreover, PET was able to detect additional sites of disease in 39.4% of patients. PET can thus improve the classification of patients into curative and palliative categories. Trends toward inferior disease-free survival and lower complete response rates in patients with additional lesions detected on PET have been demonstrated. This indicates that PET has a significant impact on management and outcomes in patients with head and neck cancer.
- Monitoring response to treatment is another possible application of PET. It provides a functional imaging that is rapid, reproducible, and a non-invasive *in vivo* assessment and quantification of several biologic processes. PET is useful in a variety of clinically relevant applications, including distinguishing between radiation necrosis and tumor recurrence, determining the resectability of a recurrent tumor, and evaluating response to therapy. FDG-PET has demonstrated efficacy for monitoring therapeutic response in a wide range of cancers, including head and neck cancer. Following therapy, the decrease of glucose use correlates with the reduction of viable tumor cells. FDG-PET allows the prediction of therapy response early in the course of therapy and the determination of the viability of residual masses after treatment completion. The molecular basis for the success of FDG-PET is the rapid reduction of tumor glucose metabolism in effective therapies. Of even greater clinical relevance is the accurate identification of non-responders in patients without a significant change in tumor glucose metabolism after initiation of therapy. PET imaging can easily visualize these changes in metabolic activity and indicate, sometimes within hours of the first treatment, whether or not a patient will respond to a particular therapy. One of the major limitations for the routine application of FDG-PET imaging for therapy monitoring is that no generally accepted cutoff values have been established to differentiate optimally between responders and non-responders.
- Although PET has been used in different tumor types for detection of recurrent disease, data in head and neck cancer are not yet available.
- Hypoxia is a negative prognostic factor and PET can be used to show hypoxia for which different tracers have been developed. 18F-fluoromisonidazole (FMISO) and FDG-PET show a low correlation with other techniques to demonstrate hypoxia; each approach has methodological limitations and validation of these techniques is necessary.
- The evaluation of the proliferation fraction in head and neck cancer tumors was done by 18F-FLT and the prognostic meaning of tumoral FLT-uptake has been tested in a small set of patients with head and neck cancer. 18F-FLT did not provide additional visual information in comparison to FDG-PET, while 18F-FLT uptake was inversely correlated with patient survival.

In the future PET might be used for more than staging purposes alone and it may have a place in determining prognosis in patients with head and neck cancer. However, good clinical studies are necessary for a definite answer.

Treatment selection and quality control

Radiotherapy

Several radiotherapy studies looked at improvement of treatment results by changing radiotherapy fractionation or adding drugs. They were discussed and placed in the context of actual knowledge.

- B. Zackrisson presented the results from a 2-year Swedish study on conventional versus accelerated radiotherapy in head and neck cancer. They could not show an improvement in overall survival or locoregional control, while acute and late toxicity were similar. This study was performed according to an intensive quality assurance program that monitored the treatment process centrally. The study was placed into context of the actual knowledge based on the MACH-HN meta-analysis, that showed that there was a significant survival benefit with altered fractionated radiotherapy, corresponding to an absolute benefit of 3.4% at 5 years (hazard ratio 0.92, 95%CI 0.86-0.97; p=0.003). The benefit was significantly higher with hyperfractionated radiotherapy (8% at 5 years), than with accelerated radiotherapy (2% with accelerated fractionation without total dose reduction, and 1.7% with total dose reduction at 5 years, p=0.02). There was a benefit on locoregional control in favor of altered fractionation versus conventional radiotherapy (6.4% at 5 years; p<0.0001), which was particularly efficient in reducing local failure, whereas the benefit on nodal control was less pronounced. However, the quality of radiotherapy of the studies included in the meta-analysis was not independently evaluated, possibly explaining the difference in the results of the presented data.
- The importance of such quality control was shown

by L. Peters, et al, in the HeadSTART study. They reviewed the radiotherapy protocol compliance in 687 of 853 patients included in a study involving a hypoxic agent. They showed that there was a major protocol non-compliance overall rate of 25.4%, impacting the outcome of the treatment.

- Bourhis, et al. reported on the addition of chemotherapy to accelerated radiotherapy and compared this regimen with conventional chemoradiation and accelerated radiotherapy alone. They could not show a difference in progression-free survival between the 2 chemotherapy arms, which were better than the accelerated radiotherapy alone arm. There was no difference among the 3 arms in overall survival and loco-regional control, although the conventional chemoradiation arm was less toxic than the other 2 arms in relation to acute toxicity. He concluded that conventional chemoradiation provides the best efficacy/tolerance ratio.
- V. Gregoire reported on the combination of gefitinib with chemoradiation in a complex phase II design. The addition of gefitinib did not lead to an improvement of 2-year locoregional control when given concomitantly with chemoradiation or in the adjuvant setting. There was a high number of toxic deaths in this study, indicating that the addition of targeted agents to classical treatments is not without danger.

Surgery

The surgical management of the neck was addressed by J. Werner. Metastatic disease in the lymph nodes of the neck is an independent prognostic factor in head and neck cancer. He stated that there are many unanswered questions on the role of selective neck dissections for positive N disease. A selective neck dissection may have a place in selected patients, who classically would be treated by a radical neck dissection that consists of resection of all lymph nodes from level I-V together with the accessory nerve, internal jugular vein, sternocleidomastoid muscle and various other structures in a single block. New developments include preservation of the accessory nerve in selected patients, elective neck dissection performed in association with resection of various primary tumors, bilateral neck dissection and limited neck dissection. Werner discussed the concept of selective neck dissection, consisting of resection of only the nodal groups at greatest risk for metastasis from a given primary site. This technique is now widely employed for properly selected and elective patients, therapeutic treatment and staging of the neck, and has been proposed for limited cervical recurrences after various chemoradiation protocols. Prospective studies have demonstrated similar rates of neck recurrence and survival after elective selective neck dissection compared to elective modified radical neck dissection.

H. Langendijk discussed the prediction and prevention of swallowing dysfunction after curative radiotherapy or chemoradiation. He investigated the impact of treatment-related toxicity on health-related quality of life (HRQoL) among 425 disease-free patients with SCCHN. Toxicity was scored according to the European Organisation for Research and Treatment of Cancer (EORTC)/Radiation Therapy Oncology Group (RTOG) late radiation-induced morbidity scoring system. HRQoL was assessed using the EORTC Quality of Life Questionnaire C30. Patients were assessed at 6, 12, 18, and 24 months after completion of treatment. Of the 6 RTOG scales investigated, two significantly affected self-reported HRQoL, salivary gland (RTOG(xerostomia)) and esophagus/pharynx (RTOG(swallowing)). Although xerostomia was reported most frequently, HRQoL was most affected by swallowing, particularly in the first 18 months after completion of radiotherapy.

He also showed the development of a predictive model for swallowing dysfunction after curative radiotherapy or chemoradiation that was developed in 529 patients with SCCHN. The factors identified as independent prognostic factors for swallowing problems at 6 months were T3-T4, bilateral neck irradiation, weight loss prior to radiation, oropharyngeal and nasopharyngeal tumors, accelerated radiotherapy and concomitant chemoradiation. He presented a Dysphagia Risk Score (TDRS) that is a simple and validated measure to predict swallowing dysfunction after curative (chemo) radiotherapy.

He also discussed the development of new radiation-induced delivery techniques that spare the anatomic structures that are involved in swallowing in order to prevent late swallowing problems.

W. Woisard addressed the issue of speech and communication in patients with head and neck cancer. She stressed the importance of difference in the use of specific syllables and their importance among different languages. Methods to evaluate speech should take these differences into account. She stressed the importance of a basic protocol to reach better agreement and uniformity concerning the methodology for functional assessment of pathologic voices. A multidimensional set of minimal basic measurements suitable for all "common" dysphonias was proposed that included five different approaches: perception (grade, roughness, breathiness), videostroboscopy (closure, regularity, mucosal wave and symmetry), acoustics (jitter, shimmer, Fo-range and softest intensity), aerodynamics (phonation quotient), and subjective rating by the patient. The Voice Handicap Index (VHI) and several voice laboratory measurements were shown to be tools for multidimensional voice assessment. The following parameters can be examined: minimum frequency, maximum frequency, range, minimum intensity, subglottic pressure, mean flow, maximum phonation time, jitter, and dysphonia severity index. There was a poor correlationship between the VHI and all the scores except the emotional one (total and subscales). She concluded that the VHI and the

laboratory measurements do give independent information and can be employed in practice.

S. Singer discussed the importance of quality of life and mental well-being of head and neck cancer patients. She stressed the importance of the expectation of the patient for a certain treatment outcome and the subsequent quality of life. This may give an explanation of her findings that patients with a total laryngectomy had a better Health Related Quality of Life (HQoL) than patients with a partial laryngectomy.

- A reanalysis of data of two multi-institutional cross-sectional studies in 218 laryngectomees and 153 partial laryngectomy patients used the general and the head- and neck-specific quality of life questionnaires of the EORTC (EORTC QLQ-C30 and EORTC QLQ-H&N35). Patients with a laryngectomy were more affected in their sense of smell and, among irradiated patients, functioning levels and many symptom scales showed worse results. From her data, postoperative radiotherapy seemed to have the greatest impact on patients' HRQL that was independent of other clinical factors following surgery for laryngeal carcinoma. A subset of 86 patients was analyzed on the basis of matched pairs (matching criteria: sex and tumor stage); this analysis showed that the senses of smell and taste of the laryngectomized patients were more affected. Other domains of quality of life did not differ significantly between the groups. The subjective assessment of voice intelligibility led to worse results among the patients with partial laryngectomy, although the objective test proved the contrary. Therefore, subjective and objective assessment of quality of life can differ, which led to paradoxical results, especially for voice intelligibility. This might be due to the fact that partially resected patients have higher expectations of their operation.
- She also examined the success of voice rehabilitation in 190 patients after laryngectomy. It was assessed by speech intelligibility, measured with the postlaryngectomy-telephone-intelligibility-test, and correlated with psychosocial parameters. She found that low speech intelligibility is associated with reduced conversations and social activity. Patients are more likely to talk with an esophageal voice when their motivation for learning the new voice is high and when they assess their speech therapist as important for their motivation. The risk to communicate merely by whispering was higher when patients lived together with a partner, when they seldom spoke, and when they were not very active in social contexts. She showed that psychosocial factors could only partly explain how voice rehabilitation after laryngectomy becomes a success. Speech intelligibility is associated with active communication behavior, whereas the use of an esophageal voice is correlated with motivation.

When patients were asked to whom they would like to talk about their psychological issues, most of them stated that their physician would be the preferred person, although this is not perceived by the physician as such: 83 % of the patients asked for psychosocial help from the treating physician, 44 % from the social worker, 30 % from the clinical psychologist, and 8 % from a spiritual adviser. The majority of patients would like to get psychosocial support, especially from their treating physician. It should be recognized that it is not only palliative care patients with advanced disease who need psychosocial treatment and support.

Recurrent and/or metastatic disease

In patients with recurrent and/or metastatic disease, the issue of salvage surgery, salvage radiotherapy and the place of chemotherapy were discussed.

P. Nicolai showed his experience in the management of radiotherapy failures using endoscopic resection with carbon dioxide laser (ER), open-neck partial laryngectomy (ONPL), and total laryngectomy. In patients with a glottic rT1a, rT1b with limited anterior commissure involvement, and rT2 with normal cord mobility carcinoma, ER resection was performed. ONPLs were performed for rT1 and rT2 tumors with suboptimal endoscopic exposure, rT2 tumors with impaired cord mobility or transcommissural extension, and rT3 tumors for limited paraglottic space invasion or involvement of the inner portion of the thyroid cartilage. A total laryngectomy was performed in patients who were not suitable for partial laryngectomy owing to poor general condition, for rT3 carcinoma with massive involvement of the paraglottic space, and for rT4a tumors. Salvage surgery was possible in most patients, except those who refused or had unfit conditions. The 5--year disease-specific and disease-free survival and laryngeal preservation were 72%, 61%, and 40%, respectively. He concluded that salvage surgery is a valid method in patients with localized recurrent disease and that in selected patients larynx preservation can be achieved.

E. Lartigau looked at the possible role of stereotactic radiotherapy for salvage re-irradiation in patients with recurrent, inoperable SCCHN. In clinical studies of re-irradiation in the 1980s, repeat courses of radiation of 60 Gy with total doses exceeding 120 Gy were associated with low rates of severe complications, but death as a result of bleeding was reported in 4-10% patients. Reported rates of osteo-radionecrosis, severe fibrosis, soft tissue necrosis, and mucosal necrosis appear to be surprisingly uncommon after re-irradiation compared with studies of primary radiation. However, rigorous late effects assessment and reporting is particularly challenging in patients with head and neck cancer, who are likely to harbor high rates of cumulative effects from multiple therapies. Accurate estimation of late injury is also difficult because of the small numbers of survivors. Vascular stenosis and thrombo-embolism are

potential late complications of head and neck radiation that can manifest as transient ischemic events, ischemic stroke, or amourosis fugax. A heightened risk of vascular stenosis and thrombo-embolic events would therefore be expected following re-irradiation but these events have not been reported. This is possibly because this entity is both under-appreciated and under-reported. Issues regarding quality of life and functional impairment (e.g. eating, nutrition, speech, pain, fatigue) are important in weighing the benefit of re-irradiation and further studies are needed.

A method to decrease the complication rate may be the use of stereotactic radiotherapy. One such method is the use of CyberKnife radiosurgery. In a small sample of patients, total doses of 18-40 Gy were administered in 3 to 5 fractions for 3-5 consecutive days. With this technique, complete responses up to 40% have been reported in selected patients with late complications such as bone and soft tissue necrosis. Fractionated stereotactic radiosurgery can be an effective treatment modality as a salvage treatment with good short-term local control. However, more data and a longer follow-up are necessary to determine the role of fractionated stereotactic radiosurgery as a salvage treatment of locally recurrent head and neck cancer and to define long-term complications.

M. Merlano discussed the role of palliative drug treatment and the role of chemotherapy in patients with recurrent head and neck cancer. In patients with recurrent disease, response rates for single agent treatments vary from 10-20%; combination platinum-based chemotherapy yield higher response rates up to 35-40%. However, with both treatments, the median survival is between 5 and 9 months; long-term survivorship is poor, with less than 5% of patients alive beyond 5 years. The monoclonal antibody cetuximab showed for the first time a survival benefit in patients with recurrent and/or metastatic head and neck cancer.

Chemotherapy should be used in selected patients who do not have significant co-morbidity, while palliative care should be an integral part of the treatment and care strategy.

Elderly patients

The management of elderly patients was discussed in a separate symposium. L. Balducci discussed the problems that elderly patients face. Not only does the chronological age determine the life-expectancy of these patients, but also the co-morbidity has an important impact on the further outcome of elderly patients. When discussing treatment, these factors should be taken into account and attention should be given not to harm the elderly patient by causing morbidity and mortality due to excessive and sometimes toxic treatments.

C. Leemans looked at the importance of co-morbidity in relation to surgery in patients with head and neck cancer. He showed the impact of co-morbidity on the survival of patients undergoing composite resection and microvascular reconstruction for oral/oropharyngeal cancer. Co-morbidity was graded by the Adult Co-morbidity Evaluation (ACE-27) test and ACE-27 grade 3 turned out to be a clear predictor for overall survival ($p<0.05$). For ACE-27 grade 3 patients, the 5-year survival was 29%, and for ACE-27 grade 2 patients it was 64%. He concluded that improved knowledge of the effect of co-morbidity on survival may lead to better patient selection and counseling for major surgery and microvascular reconstruction.

J. Overgaard looked at the results of the Danish Head and Neck Cancer Study (DAHANCA) data on elderly patients. He showed that elderly patients are relatively underrepresented in these trails. However, when they comply with the inclusion and exclusion criteria, there seems to be less benefit from intensified radiotherapy schedules in elderly patients than in younger patients. This is confirmed by recent meta-analyses: the hazard ratio was 0.78 (95%CI 0.65-0.94) for patients under 50 years old; 0.95 (95%CI 0.83-1.09) for those 51-60 years old; 0.92 (95%CI 0.81-1.06) for those 61-70 years old; and 1.08 (95%CI 0.89-1.30) for patients over 70 years old (test for trends $p=0.007$). The toxicity was similar among age groups. He concluded that more studies are needed in the population in which a specific tumor is occurring and that, for head and neck cancer, the elderly patients are not the target population.

Finally L. Balducci discussed the role of chemotherapy in elderly patients. When giving these treatments, it is important to take the age-related changes in metabolism and distribution into account. He stressed the importance of specific treatments in the elderly population which, at the moment, are lacking for elderly head and neck cancer patients.

Evidence-based medicine

Finally, the importance of evidence-based data was discussed in the last session. The role of partial surgery as an organ preservation strategy in laryngeal cancer was discussed by J. Rodrigo Tapia. He stressed that, in most organ preservation trials, there is no arm of partial surgery; laryngectomy is compared with chemoradiation or radiotherapy. In several small studies, partial laryngectomy was shown to be curative in selected patients, and yielded long survival and adequate organ function. He concluded that there is need for randomized trials including partial surgery in the control arm.

R. Corvo stated that the newer tissue-sparing radiotherapy techniques should be the new standard arm for radiotherapy studies. New radiotherapy techniques such as intensified-modulated radiotherapy (IMRT) and tomotherapy are able to prevent partial xerostomia, as shown in randomized trials. However, the treatment outcome in relation to tumor control has never been studied. J. Overgaard replied that the radiotherapists should do their homework before stating that the new techniques should be the standard treatment.

C. Merlano summarized the state of the art of chemotherapy in patients with head and neck cancer, based on the multiple randomized trials that have been recently published.

In patients with a loco-regional advanced operable cancer, adjuvant chemoradiation after surgery is indicated for patients with bad prognostic factors. In patients where organ-preservation is indicated, concomitant, sequential or alternating chemoradiation, or bioradiation have a proven benefit compared to radiotherapy alone. In patients with inoperable disease, induction chemotherapy followed by radiotherapy or chemoradiation is better than no induction treatment. Finally in patients with metastatic and/or recurrent disease, cetuximab is able to prolong survival.

The conference did give a good overview of the current treatment of patients with head and neck cancer and new promising perspectives for the future. In 2011 the third conference is planned.

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