EJC SUPPLEMENTS 10, NO. 1 (2012) 76–81

available at www.sciencedirect.com

From chemoprevention and organ preservation programs to post-operative management: major achievements and strategies of the EORTC Head and Neck Cancer Group

J.A. Langendijk[a,*], *L. Licitra*[b], *A. Psyrri*[c], *R. Knecht*[d], *G. Andry*[e], *C. Fortpied*[f], *R. Karra Gurunath*[f]

[a] *University Medical Center Groningen, University of Groningen, Groningen, The Netherlands*
[b] *Instituto Nazionale Tumori, Milan, Italy*
[c] *Attikon Hospital, National Kapodistrian University of Athens, Greece*
[d] *Universitaets-Krankenhaus, Eppendorf, Hamburg, Germany*
[e] *Institut J. Bordet, Brussels, Belgium*
[f] *EORTC Headquarters, Brussels, Belgium*

ARTICLE INFO

Keywords:
Larynx preservation
Induction chemotherapy
Post-operative chemoradiotherapy

1. Introduction

Head and neck cancer, mostly of squamous cell origin, ranks sixth among the most common cancers, accounting for approximately 6% of all cases of cancer. Each year, more than 500,000 new cases are diagnosed worldwide.[1] Approximately 60% of patients present with advanced disease (stages III and IV), for which the prognosis is poor.[2] The multimodal curative standard treatment of squamous cell carcinoma of the head and neck (SCCHN) includes surgery followed by adjuvant treatment (radiotherapy ± chemotherapy) or primary radiotherapy in combination with chemotherapy (concurrent chemoradiation or induction chemotherapy) and/or targeted therapy. Despite this multimodality intensified approach, more than 50% of patients with locally advanced SCCHN will relapse.[3,4]

The European Organisation for Research and Treatment of Cancer (EORTC) has been at the forefront of oncology practice-changing trials throughout the world. The EORTC Head and Neck Cancer Group (HNCG) was one of the earliest EORTC disease-oriented groups to be formed. The aim of the HNCG is to develop, conduct, coordinate and stimulate clinical and translational research, in head and neck cancer patients. The HNCG mainly conducts multicenter prospective, randomized studies that will potentially change clinical practice. The HNCG comprises a well-balanced team representing all medical specialties involved in head and neck cancer treatment, including surgical oncology, maxillofacial surgery, radiation oncology, medical oncology, pathology, and radiology. This ensures and promotes harmonization of all treatment modalities that can be offered to patients.

The HNCG has contributed its might to practice-changing trials, and the following is a reflection on what has been achieved to date. It summarizes the landmark trials that have significantly modified the way head and

* Corresponding author. J.A. Langendijk.
Tel.: +31 50 3615532; fax: +31 50 3611692.
E-mail address: j.a.langendijk@umcg.nl (J.A. Langendijk).

neck cancer is understood and treated and have had a beneficial impact for the patients.

2. Major advances

2.1. Larynx preservation

The HNCG was a pioneer in the field of organ preservation starting with the initiation of the first larynx preservation trial (EORTC 24891). In 1986, the HNCG initiated this randomized phase III trial in order to investigate if larynx preservation could be achieved among patients with histologically proven squamous cell carcinomas of the piriform sinus or aryepiglottic fold without hampering overall survival (OS). Preliminary results were published in 1996 in a landmark paper in *J Natl Cancer Inst* and the 10-year results were presented as an abstract at ASCO 2004. [5]

In this study, a total number of 202 patients were randomly assigned to receive either the standard approach at that time, which was primary surgery consisting of total laryngectomy with partial pharyngectomy and neck dissection followed by post-operative radiotherapy, or the larynx preservation approach, including induction chemotherapy by two cycles of induction chemotherapy (cisplatin 100 mg/m^2 on day 1 and 5-fluorouracil [5-FU] 1000 mg/m^2 on days 1–5) followed by a third cycle in case of partial of complete response and subsequently followed by conventional radiotherapy for complete responders and conventional surgery followed by post-operative radiotherapy in case there was no complete response. The endpoints were OS, non-inferiority [hazard ratio (preservation/surgery) $\leqslant$1.43, 1-sided $\alpha = 0.05$], progression-free survival (PFS), and survival with a functional larynx (SFL).

At a median follow-up of 10.5 years, there were 194 eligible patients included in the analysis. Disease progression was seen in 54 and 49 patients in the surgery and larynx preservation arm, and 81 and 83 patients had died, respectively. The 10-year OS rate was 13.8% in the surgery arm and 13.1% in the preservation arm. The 10-year PFS rates were 8.5% and 10.8%, respectively. Most importantly, in the entire group of 100 patients included in the larynx preservation arm, the rates of patients with a functional larynx were 42% and 35% at three and five years, respectively.

This first randomized trial on induction chemotherapy for larynx preservation in advanced but resectable hypopharyngeal cancer has shown that larynx preservation in locally advanced hypopharyngeal cancer is feasible without jeopardizing OS. In addition, the EORTC adopted induction chemotherapy followed by radiotherapy as the new standard for the next EORTC study on larynx preservation.

In addition to this study, the HNCG conducted a second larynx preservation study (EORTC 24954) in which patients with resectable advanced squamous cell carcinoma of the larynx or hypopharynx were randomly assigned to receive sequential chemotherapy followed by conventional radiotherapy (as described above) or alternating chemoradiation, consisting of four cycles of cisplatin (100 mg/m^2 per day) and 5-FU (200 mg/m^2 per day instead of 1000 mg/m^2 per day) in weeks 1, 4, 7, and 10 alternated with radiotherapy with 20 Gy during the three 2-week intervals between chemotherapy cycles to a total dose of 60 Gy. In this study, the control arm was the same as the experimental arm of EORTC protocol 24891, except that there were four cycles of chemotherapy instead of three cycles. All non-responders underwent salvage surgery and post-operative radiotherapy. [6]

In this study, a total number of 450 patients were randomly assigned to either sequential or alternating chemoradiation. The primary endpoint of this study was SFL in place. After a median follow-up of 6.5 years, there was a non-significant trend towards better outcome for the alternating arm. The 3-year SFL was 39.5% for the sequential arm and 45.4% for the alternating arm. The 5-year SFL was 30.5% for the sequential arm and 36.2% for the alternating arm. No significant difference was found between the two arms with regard to OS. Grade 3 or 4 mucositis occurred in 32% of the 200 patients in the sequential arm who received radiotherapy and in 21% of the 220 patients in the alternating arm. Late severe oedema and/or fibrosis were observed in 16% of the patients in the sequential arm and in 11% in the alternating arm.

Based on these findings, it was concluded that larynx preservation, progression-free interval, and OS were similar in both arms, as were acute and late toxic effects.

2.2. Induction chemotherapy

In the 1990's, the results of phase II studies indicated that docetaxel plus cisplatin and fluorouracil (TPF) might be more efficacious than the classic regimen of cisplatin plus fluorouracil (PF). Therefore, the EORTC Head and Neck Cancer Group conducted the EORTC 24971/TAX 323 study, comparing TPF with PF induction chemotherapy followed by conventional radiotherapy in patients with locoregionally advanced, unresectable squamous-cell carcinoma of the head and neck. The results of this landmark study were published in 2007 in the *New England Journal of Medicine*. [4]

In this study, patients were randomly assigned to receive either TPF or PF. The TPF regimen consisted of docetaxel at a dose of 75 mg/m^2 administered as a 1-hour infusion on day 1, followed by cisplatin at a dose of 75 mg/m^2, administered as a 1-hour infusion on day 1, and fluorouracil at a dose of 750 mg/m^2 per day, administered by continuous infusion on days 1–5. The PF regimen consisted of cisplatin at a dose of

100 mg/m^2, administered as a 1-hour infusion on day 1, followed by fluorouracil at a dose of 1000 mg/m^2 per day, administered by continuous infusion on days 1–5. Treatment was administered every 3 weeks (defined as one cycle) for up to 4 cycles, unless progressive disease, unacceptable toxic effects, or withdrawal from the study occurred earlier. During chemotherapy, patients were monitored clinically and with laboratory tests on day 1 of each cycle before treatment. Imaging of tumours was performed at the end of cycles 2 and 4.

Patients who did not have progressive disease and who had adequate bone marrow function (neutrophil count $\geqslant 2.0\times10^3$ cells/mm^3; platelet count $\geqslant 100\times10^3$ cells/mm^3; and hemoglobin $\geqslant$10 g/dl), complete resolution of mucositis for at least one week, and healing from any dental procedures, underwent radiotherapy within 4–7 weeks after the completion of chemotherapy. Radiation was delivered during a 7-week period with the use of either conventional fractionation (total dose, 66–70 Gy) or accelerated or hyperfractionated regimens (total maximum dose of 70 Gy for the accelerated regimen and 74 Gy for the hyperfractionated regimen).

The primary endpoint of this study was PFS. Secondary endpoints were OS, best overall response rate after induction chemotherapy and after radiation therapy, duration of response, time to treatment failure, toxic effects, and health-related quality of life, as reported previously.

This study showed that TPF induction chemotherapy resulted in significant and clinical meaningful improvements in outcomes, as compared with PF induction chemotherapy, in locoregionally advanced, unresectable SCCHN. Patients who were treated with TPF had a reduction of 28% in the risk of disease progression or death, as compared with those who received PF. They also had an extension of 2.8 months in median PFS. This result was associated with significant improvements in OS, overall response rates, and time to treatment failure. Patients in the TPF group had a reduction of 27% in the risk of death, an improvement in median OS of 4.3 months, and an absolute increase in 3-year survival of 10.9%.

2.2.1. *Long-term follow up*

Recently, long-term data were collected and analyzed using the Cox proportional hazard model adjusted for treatment, tumor site, T-classification, N-classification and performance status. In this updated analysis, the PFS remained significantly better with TPF compared with PF (hazard ratio [HR] unadjusted 0.71 [95% CI: 0.57–0.89], p = 0.003, medians of 12.7 *versus* 8.6 months, and 5-year PFS 22.9% *versus* 13.5%, mainly due to less locoregional progression). A similar picture was observed for OS (HR unadjusted 0.74 [95% CI: 0.59–0.94], p = 0.011, medians of 18.8 *versus* 14.5 months, 5-year OS 27.5 *versus* 18.6%).

Long-term side effects in the TPF *versus* PF arm were: 7.3% *versus* 5.0% for tracheotomy; 3.4% *versus* 5.5% feeding tube dependence; 10.7% *versus* 10.5% for gastrostomy, and 7.9% *versus* 3.3% for second malignancies.

The long-term data on survival and long-term side effects (feeding tube dependency, tracheotomy, gastrostomy and second malignancies) with a median follow-up of 8.6 years were presented at ASCO 2011. The results consistently showed survival advantage for the TPF arm and supported the conclusions of the final analysis that TPF is superior to PF as induction chemotherapy regimen for patients with unresectable SCCHN.

2.3. *Post-operative chemoradiotherapy*

The HNCG also pioneered the concept of post-operative chemoradiation for treatment of stage III or IV resected head and neck cancer. This trial, EORTC 22931, was published in the *New England Journal of Medicine* in 2004. [7] The primary objective of this study was to investigate the additional value of concomitant chemotherapy to standard post-operative radiotherapy.

In this phase III study, a total number of 334 patients with curatively resected SCCHN were randomly assigned to receive post-operative radiotherapy alone (66 Gy over a period of 6 weeks) or the same post-operative radiotherapy regimen combined with concurrent chemotherapy consisting of cisplatin (100 mg/m^2 on days 1, 22, and 43 during radiation). The primary endpoint was PFS.

After a median follow-up of 60 months, the 5-year PFS was 47% after post-operative chemoradiation which was significantly better than the 36% observed after post-operative radiotherapy alone (P = 0.02; HR 0.75 [95% CI: 0.56–0.99). In addition, the OS rate was also significantly higher in the chemoradiation group than in the radiotherapy group (P = 0.04; HR for death, 0.70; 95% CI: 0.52–0.95), with 5-year Kaplan–Meier estimates of OS of 53% and 40%, respectively. The cumulative incidence of local or regional relapses was significantly lower in the combined-therapy group (P = 0.007). The estimated 5-year cumulative incidence of local or regional relapses (considering death from other causes as a competing risk) was 31% after radiotherapy and 18% after combined therapy. Severe (grade 3 or higher) adverse effects were more frequent after combined therapy (41 percent) than after radiotherapy (21 percent, P = 0.001); the types of severe mucosal adverse effects were similar in the two groups, as was the incidence of late adverse effects.

The results confirmed that post-operative concurrent administration of high-dose cisplatin with radiotherapy is more efficacious than radiotherapy alone in patients with locally advanced head and neck cancer, and does not cause an undue number of late complications. The results of this study were combined with those from a similar study conducted by the RTOG (RTOG study 9501) in a joined analysis, which showed that the addition of

concomitant chemotherapy in the post-operative setting was particularly efficacious in case of positive surgical margins and/or lymph node metastases with extranodal spread, which has now become the current standard in these cases. [8]

3. Translational research

The HNCG has a good translational research (TR) component exploring the various molecular mechanisms underlying SCCHN as well as the predictors for response and resistance. Tissue banks from large prospective clinical trials, such as those conducted by EORTC, represent precious resources for validation of biomarkers before their clinical implementation. EORTC has developed standardized protocols for specimen collection, processing, and storage.

In the previous decades SCCHN was regarded as a single disease entity. However, advances in molecular biology tools with the widespread application of genomic and proteomic approaches have revealed that distinct prognostic subclasses exist beyond those defined by TNM stage. [9] For example, several lines of epidemiological, molecular pathology and experimental evidence suggest that Human Papillomavirus (HPV), especially type 16, are causally associated with a subset of oropharyngeal squamous cell carcinomas. [10] HPV-associated SCCHN represent a distinct clinical entity in terms of biology and clinical behaviour. HPV-associated SCCHN expresses E6 and E7 viral oncoproteins which bind and degrade p53 and retinoblastoma (pRb) tumor suppressor proteins, respectively. A negative autoregulatory loop between p16 and pRb has been reported; low pRb protein levels of HPV-induced tumors lead to p16 protein overexpression. Therefore, HPV-associated SCCHN contain high p16 protein levels. p16 positivity is used as a surrogate marker for biologically and clinically meaningful HPV infection. [11] From the clinical perspective, HPV positivity confers 50–80% reduction in risk of disease failure compared to tobacco-associated SCCHN. [12–14] The contribution of therapy selection in the observed survival benefit, however, is unclear. Therefore, it is possible that patients with HPV-associated SCCHN are exposed to unnecessary overtreatment. Clinical trials studying treatment deintensification in the HPV-positive subgroup are currently being undertaken. In this context, several TR projects are planned by HNCG. First, we plan to retrospectively analyze oropharyngeal cancer specimens from patients included in the EORTC 24971 for tumor HPV and p16 status and to correlate results with treatment outcome per study arm. This retrospective analysis will hopefully provide us with valuable results that will be validated in the setting of a prospective trial. The question we aim to answer is whether the addition of docetaxel to PF provides additional benefit in the HPV+/p16+ patient subgroup. Patients participating in the EORTC 22071–24071 post-operative study will be subjected to prospective p16 determination to demonstrate whether p16+ patients with high risk features derive survival gain with the incorporation of panitumumab to standard post-operative cisplatin chemoradiotherapy.

Epidermal growth factor receptor (EGFR) signaling network is pivotal for SCCHN growth and survival. [15–17] Despite the vast amount of experimental and clinical evidence supporting the use of EGFR-targeted therapy in SCCHN, single-modality treatment with these agents in unselected clinical trials is associated with modest results. The most intriguing research question in EGFR-targeted therapy in SCCHN is patient selection. Mechanisms of resistance to EGFR-targeted therapies have been identified in other tumors. In colon cancer, for example, *KRAS* mutations are associated with resistance to cetuximab and panitumumab. The HNCG has initiated window of opportunity studies that will serve as a platform to identify new relevant molecular targeted therapies in SCCHN and to collect biological samples to better understand treatment resistance. For this purpose, new promising compounds will be tested in the pre-operative window setting to resolve some of these issues and maximize the chance of observing tumor response. In addition, the collection of biopsies before treatment at the time of diagnosis and after treatment at the time of surgery will permit the assessment of predictive molecular markers and may help in identifying subgroups of patients most likely to respond to therapy.

Genetic factors may affect response or toxicity to chemotherapy and radiotherapy. Platinum is widely used to treat SCCHN although a substantial proportion of patients fail to respond to treatment, and initial responders remain at risk for disease progression or recurrence. Genetic variations that play a role in cellular repair of drug-induced DNA damage may affect patient response to chemotherapy. Understanding these variations may improve outcomes by allowing oncologists to optimize treatment based on each patient's genetic and molecular background. Excision repair cross-complementation group 1 (ERCC1) is a DNA repair gene in the nucleotide excision repair (NER) pathway that is activated when platinum-based chemotherapy drugs, such as cisplatin and carboplatin, form DNA adducts. The relation between *ERCC1* mRNA and protein expression and resistance to platinum has been demonstrated in prospective and retrospective studies in patients with advanced-stage gastric, ovarian, colorectal, esophageal, and non-small-cell lung cancers but it has not been clearly shown in SCCHN. The HNCG is planning to determine the impact of ERCC1 gene polymorphisms and protein expression on PFS of patients who participated in the EORTC 22931 phase III clinical trial.

In addition to aforementioned projects, several other TR proposals will be conducted in the future on

biospecimens of the tissue banks from prospective studies. The aim is to shed light to the biology of the disease, identify prognostic subclasses and predictors for response or toxicity to therapy in order to increase cure rates.

4. Collaborations with other groups in intergroup studies

Joint sessions with the EORTC Radiation Oncology Group during the EORTC Groups Annual Meetings are currently standard. A fruitful discussion with the members of the EORTC Radiation Oncology Group resulted in several common proposals with this group. In addition, a number of meetings have taken place between representatives of both groups, which resulted in new plans for future collaborations.

There is an ongoing collaboration with other groups within the EORTC frame work. Since 2008, the HNCG meetings started with specific subcommittee meetings for translational research, imaging and quality of life. The main objective of these sessions was to enhance the collaboration with other groups and to stimulate integration of additional studies to the phase II and phase III studies under construction. More specifically, a number of translational research projects have been conducted by the group using either information from existing databases of former clinical studies or data that will be derived from future clinical studies. Together with the EORTC Imaging Group, the aim is to conduct add-on studies to future phase III studies. Finally, the group collaborates with the EORTC Quality of Life Group on the development of a new and revised version of the head and neck quality of life module to assess quality of life.

5. Future strategy

The HNCG has developed strategies to promote patient-oriented laboratory research, and they recently summarized ongoing and planned clinical trials, outlined planned translational research projects, and described strategies to promote translational head and neck cancer research, which will include the following issues for future clinical studies:

- There will be a close collaboration with the EORTC Radiation Oncology Group, in particular for new studies in the primary setting in which radiotherapy is part of the treatment regimens. In particular, the EORTC Radiation Oncology Group will play an important role in Quality Assurance of radiotherapy in all future clinical studies;
- Prospective tissue collection and biobanking from patients treated in future clinical trials will be routinely performed for translational research purposes, e.g. in order to identify prognostic and in particular predictive factors and to generate hypotheses for future clinical trials in SCCHN;
- In order to do this efficiently, increased collaboration between the basic scientists of the EORTC Translational Research Division interested in head and neck cancer research and the physicians of the HNCG will be enhanced;
- The initiation of trials with novel methodology like windows of opportunity study will test the feasibility, efficacy and safety of targeted agents in the pre-operative setting;
- HPV-positive SCCHN should be considered a separate entity with a more favourable prognosis than the HPV-negative subpopulation. For patients with HPV-positive oropharyngeal cancer, future trials will focus on the development of less toxic regimens with similar efficacy, either in collaboration with other international groups or within the EORTC framework using alternative statistical study designs. For the subset of patients with HPV-negative tumors, separate trials will be conducted in which the value of new regimens containing taxanes and EGFR-inhibitors combined with modern radiation techniques will be further explored;
- Given the results obtained among patients at intermediate risk after primary surgery and given the number of patients that can be included in such studies, it will be unlikely that phase III studies in the intermediate-risk subset will be feasible from a statistical point of view. Therefore, studies in the post-operative setting will embark on the results of the EORTC 22931 and will mainly focus on the high-risk patients;
- New steps are taken to design and initiate clinical trials in rare tumors like salivary gland cancer, nasopharyngeal cancer and paranasal sinus tumors.

6. Conflict of interest statement

A. Psyrri, R. Karra Gurunath, C. Fortpied, and G. Andry declare no conflicts of interest. J.A. Langendijk consulted for Merck Serono. L. Licitra consulted for BMS, GSK, Eli Lilly, Merck Serono, Amgen, Pfizer, Oxigene, and AstraZeneca. R. Knecht advised for Sanofi Aventis, Merck, Boehringer, and Bayer.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;**55**:74–108.
2. Seiwert TY, Cohen EEW. State-of-the-art management of locally advanced head and neck cancer. *Br J Cancer* 2005;**92**:1341–8.
3. Pignon JP, le Maître A, Maillard E, Bourhis J; MACH-NC Collaborative Group. Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93

randomised trials and 17,346 patients. *Radiother Oncol* 2009;**92**(1):4–14.
4. Vermorken JB, Remenar E, van Herpen C, et al.; EORTC 24971/TAX 323 Study Group. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med* 2007;**357**(17):1695–704.
5. Lefebvre JL, Chevalier D, Luboinski B, Kirkpatrick A, Collette L, Sahmoud T. Larynx preservation in pyriform sinus cancer: preliminary results of a European Organization for Research and Treatment of Cancer phase III trial. EORTC Head and Neck Cancer Cooperative Group. *J Natl Cancer Inst* 1996;**88**(13):890–9.
6. Lefebvre JL, Rolland F, Tesselaar M, et al.; EORTC Head and Neck Cancer Cooperative Group; EORTC Radiation Oncology Group. Phase 3 randomized trial on larynx preservation comparing sequential vs alternating chemotherapy and radiotherapy. *J Natl Cancer Inst* 2009;**101**(3):142–52.
7. Bernier J, Domenge C, Ozsahin M, et al.; European Organization for Research and Treatment of Cancer Trial 22931. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;**350**(19):1945–52.
8. Bernier J, Cooper JS, Pajak TF, et al. Defining risk levels in locally advanced head and neck cancers: a comparative analysis of concurrent postoperative radiation plus chemotherapy trials of the EORTC (#22931) and RTOG (#9501). *Head Neck* 2005;**27**(10):843–50.
9. Psyrri A, Licitra L, Lacombe D, et al. Strategies to promote translational research within the European Organisation for Research and Treatment of Cancer (EORTC) Head and Neck Cancer Group: a report from the Translational Research Subcommittee. *Ann Oncol* 2010;**21**(10):1952–60.
10. Capone RB, Pai SI, Koch WM, et al. Detection and quantitation of human papillomavirus (HPV) DNA in the sera of patients with HPV-associated head and neck squamous cell carcinoma. *Clin Cancer Res* 2000;6(11):4171–5.
11. Rampias T, Sasaki C, Weinberger P, Psyrri A. E6 and E7 gene silencing and transformed phenotype of human papillomavirus 16-positive oropharyngeal cancer cells. *J Natl Cancer Inst* 2009;**101**(6):412–23.
12. Weinberger PM, Yu Z, Haffty BG, et al. Molecular classification identifies a subset of human papillomavirus-associated oropharyngeal cancers with favorable prognosis. *J Clin Oncol* 2006;**24**(5):736–47.
13. Schwartz SR, Yueh B, McDougall JK, Daling JR, Schwartz SM. Human papillomavirus infection and survival in oral squamous cell cancer: a population-based study. *Otolaryngol Head Neck Surg* 2001;**125**(1): 1–9.
14. Licitra L, Perrone F, Bossi P, et al. High-risk human papillomavirus affects prognosis in patients with surgically treated oropharyngeal squamous cell carcinoma. *J Clin Oncol* 2006;**24**(36):5630–6.
15. Grandis JR, Tweardy DJ. Elevated levels of transforming growth factor alpha and epidermal growth factor receptor messenger RNA are early markers of carcinogenesis in head and neck cancer. *Cancer Res* 1993;**53**(15):3579–84.
16. Bonner JA, Harari PM, Giralt J, et al. Radiotherapy plus cetuximab for locoregionally advanced head and neck cancer: 5-year survival data from a phase 3 randomised trial, and relation between cetuximab-induced rash and survival. *Lancet Oncol* 2010;**11**(1):21–8.
17. Vermorken JB, Mesia R, Rivera F, et al. Platinum-based chemotherapy plus cetuximab in head and neck cancer. *N Engl J Med* 2008;**359**(11):1116–27.