available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

Cetuximab combined with radiotherapy: An alternative to chemoradiotherapy for patients with locally advanced squamous cell carcinomas of the head and neck?

J. Bernier, D. Schneider*

Radio-Oncologie, Clinique de Genolier, Genolier 1272, Switzerland

ARTICLE INFO

Article history:
Received 22 August 2006
Received in revised form
23 August 2006
Accepted 24 August 2006
Available online 13 November 2006

Keywords:
Chemoradiotherapy
Cetuximab
Erbitux
Locally advanced
Radiotherapy
SCCHN

ABSTRACT

Radiotherapy remains the foundation of current treatment for patients with locally advanced squamous cell carcinoma of the head and neck (SCCHN). It has been shown that the addition of concurrent chemotherapy to radiotherapy (chemoradiotherapy, CRT, or chemotherapy-enhanced radiation therapy, CERT) results in improved clinical outcome in terms of both locoregional control and overall survival in some groups of patients. However, CRT is associated with severe, dose-limiting acute toxicities and, in some patients, a higher proportion of late toxicities. In addition, most CRT regimens are platinum-based and there is evidence that the maximum tolerable toxicity has been reached with the dose intensities currently used in bolus cisplatin regimens. Therefore, if we are to further improve outcomes through increased treatment compliance, more effective and more tolerable regimens are needed. Recent results from a phase III randomised study demonstrate that the epidermal growth factor receptor (EGFR) inhibitor cetuximab (Erbitux®) given concomitantly with radiotherapy yields a significant clinical benefit over radiotherapy alone without any increase in radiotherapy-associated toxicity. In this review, we explore the question of the degree to which adding cetuximab improves the efficacy of radiotherapy in locally advanced SCCHN and how the benefits of cetuximab plus radiotherapy compare with those achievable with CRT.

1. Treatment rationale for SCCHN

Cancers of the head and neck, primarily squamous cell carcinomas of the oral cavity, pharynx and larynx, account for over 5% of all malignancies. Worldwide, in 2002, there were in excess of 500,000 new cases and over 300,000 deaths attributed to this disease.[1]

Surgery and/or radiotherapy are commonly used to treat locally advanced disease.[2] However, a considerable proportion of patients relapse, either locally or at distant sites, following surgery.[3] In addition, the long-term treatment outcome of patients with locally advanced disease is known to be poor with conventional schedules of radiotherapy: locoregional control of the disease is seen in approximately 30% of patients,[4,5] with 5-year survival rates of only 15%–25%[6] and median survival of approximately 12 months.[7] The general lack of success associated with the range of treatments available for locally advanced SCCHN prompted the search

* *Corresponding author:* Tel.: +41 919673803; fax: +41 918118678.
E-mail address: jacques.bernier@hcuge.ch (J. Bernier).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2006.08.035

for new approaches which resulted in the development of alternative radiotherapy fractionation schedules, such as hyperfractionation and accelerated fraction with concomitant boost,[8,9] both of which have been shown to be more effective in terms of locoregional control than standard fractionation in this setting.[10]

In parallel, strategies were developed to integrate the administration of systemic chemotherapy into radiotherapy schedules, with certain of these cytotoxic agents being used as radio-sensitisers.[5,11] The rationale for this approach was based both on increasing the tumour cell kill at the local level and additionally on targeting distant micro-metastases present at the time of the primary treatment.[12] This led to the implementation of high dose-intensity regimens, which resulted in significant increases in treatment efficacy, in terms of locoregional control and survival.[5,11] However, this increase in efficacy came at the cost of increased toxicity, particularly in relation to severe acute side-effects which were seen in a significant number of patients. Consequently, poor treatment compliance is observed in around one-third of cases, commonly in those receiving cisplatin (100 mg/m^2 every 3 weeks).[5,11]

Therefore, there was a clear need to optimise treatment combinations based on drug-radiotherapy interactions and to develop protocols integrating novel, highly efficient agents able to exert synergistic effects with radiotherapy as well as increasing its selectivity index.

2. The concept of cytotoxic enhancement

In addition to the systemic effects of cytotoxic chemotherapy, the concomitant administration of chemotherapy and radiotherapy capitalises on the radiosensitising properties of standard cytotoxic agents to improve locoregional control. Throughout the last two decades, three types of combination chemotherapy and radiotherapy – neoadjuvant, adjuvant and concurrent – have been compared with radiotherapy alone. Concurrent chemoradiotherapy (CRT), also known as chemotherapy-enhanced radiation therapy (CERT),[13] has been shown to be the most effective approach, with most studies showing significant increases at 3 years in both survival and locoregional control rates when CRT is compared with radiotherapy alone.[4,14–19]

Studies have shown a clinical benefit of CRT over radiotherapy in certain groups of patients with locally advanced disease. Most studies conducted to date have used radiotherapy together with cisplatin alone or in combination with 5-FU.[4,14,15,20–22] A phase III randomised, three-arm study reported by Adelstein et al. allowed for a direct comparison of two concomitant CRT regimens (radiotherapy versus radiotherapy plus concurrent bolus cisplatin versus split course of fractionated radiotherapy and concurrent infusional FU and bolus cisplatin) in 295 patients with unresectable disease.[14] The results from this trial demonstrated the superiority of single-agent cisplatin CRT over radiotherapy alone (3-year projected overall survival 37% versus 23%, $p = 0.014$). However, the use of split-course radiotherapy with combined chemotherapy was associated with a similar survival rate to radiotherapy alone (27%), but with a significant increase in $\geqslant$grade 3 toxicity. A potential reason for the lack of benefit with the multi-agent arm is the scheduling of the split-course radiotherapy, which was designed to allow for the possibility of mid-course surgery for any patients rendered resectable by the initial CRT. Split-course radiotherapy is generally recognised as a suboptimal way of delivering radiotherapy[23] and in this case was evidently not offset by either the multi-agent chemotherapy or the possibility of mid-course surgery.[14] Furthermore, treatment compliance was poorer in the CRT/split-course arm, with 27% of the patients failing to complete treatment compared with corresponding figures of 7% in the radiotherapy arm and 15% in the radiotherapy/cisplatin arm.

In a large phase III randomised study in 270 assessable patients, the addition of cisplatin/5-FU/FA to radiotherapy significantly improved 3-year overall survival (49% versus 24%, $p < 0.0003$) and 3-year locoregional control rate (35% versus 17%, $p < 0.004$) compared with radiotherapy alone.[4] Interestingly, the proportion of distant failures was similar in each arm (approximately 9%). Several smaller, but influential, studies have also shown the efficacy of radiotherapy combined with cisplatin/5-FU in unresectable disease. A phase III study compared the survival rates in 171 patients with previously untreated, unresectable oro- and hypo-pharyngeal carcinomas, randomised to receive CRT (3 cycles of cisplatin and 5-FU plus radiotherapy) or radiotherapy alone.[20] The addition of chemotherapy to radiotherapy significantly improved the overall survival rate at 18 months (48% versus 36%, $p = 0.05$), although these benefits were mainly confined to the 123 patients with oropharyngeal carcinoma, where the median survival time was prolonged from 10 to 17 months ($p < 0.05$). In another single-arm study in 50 patients, cisplatin and 5-FU were combined with hyperfractionated radiotherapy and compared with a historical control group of 29 patients who had received radiotherapy alone.[21] With a median follow-up of 23 months, the overall 2-year survival rates were 80% and 43% ($p < 0.01$), respectively.

The use of a different chemotherapy regimen, mitomycin C plus 5-FU, added to hyperfractionated accelerated radiotherapy (C-HART) was investigated in a large phase III randomised study in 384 patients with unresectable SCCHN.[24] The use of C-HART was associated with a 5% increase in the 5-year survival rate and a 13% increase in the 5-year locoregional control rate compared with HART alone.[24] Finally, a phase III randomised study in 350 patients with locally advanced nasopharyngeal carcinoma, which compared weekly concurrent cisplatin-enhanced radiotherapy to radiotherapy alone, demonstrated a significant advantage for the cisplatin-radiotherapy over radiotherapy alone with 5-year overall survival (OS) 70% versus 59%, respectively.[25]

3. Identifying the most effective CRT regimens

The benefits of CRT compared with radiotherapy alone in some patients with locally advanced disease have also been demonstrated by meta-analyses. The update of the Meta-analysis of Chemotherapy in Head and Neck Cancer (MACH-NC) Collaborative Group's database[26] confirmed the findings of a previous, smaller analysis[27] and demonstrated a survival advantage for CRT of 5% at 5 years. This survival benefit was confined mainly to patients treated with chemotherapy administered concomitantly with radiotherapy: when data

from these patients were analysed separately from any other locally advanced treatment, the survival advantage increased to 8% at 5 years ($p < 0.0001$).

A limitation of the initial meta-analyses was that the heterogeneity of the trials and the various treatment combinations they employed hindered identification of the optimal regimen.[27] Subsequent meta-analyses identified platinum-based concomitant CRT regimens as being the most effective.[26] Interestingly, while these analyses have shown that the magnitude of benefit is significantly improved with platinum-based over other CRT regimens, they have also demonstrated that the use of multi-agent chemotherapy regimens confers no additional benefit over monotherapy.[26] Confirmation of the updated MACH-NC results comes from a review of pooled data from 18 randomised trials, involving over 3000 patients with locally advanced disease.[11] This review demonstrated an 11% reduction in the risk of death with the use of concomitant chemotherapy and radiotherapy compared with radiotherapy alone ($p < 0.00001$), and in particular that the platinum-based regimens (the most effective of the regimens used) were associated with a 12% reduction in the risk of death ($p < 0.00001$). However, the optimal chemotherapy regimen to achieve the highest possible therapeutic index remains to be determined, in terms of both the best agent(s) (cisplatin alone or in combination with 5-FU) and also the most effective dosing regimens (bolus high-dose or weekly fractionated cisplatin).

Similarly, the most effective radiotherapy schedule remains to be defined. In a retrospective analysis, hyperfractionated radiotherapy plus cisplatin showed a marginally significant improvement over conventional radiotherapy plus chemotherapy in terms of an improved overall survival, but there was no difference in locoregional control.[28] Nevertheless, a recent review of randomised trials comparing altered fractionation (AF) to CRT-AF indicated that the advantages from CRT may be greater when it is based on AF regimen.[29]

Despite the efficacy benefits of CRT in patients able to withstand this relatively aggressive type of therapy, poor compliance due to severe acute side effects in normal tissues represents a limiting factor in terms of chemotherapy and radiotherapy dose intensity.

4. The role of neoadjuvant/induction chemotherapy

Typically, neither neoadjuvant (also often referred to as induction) chemotherapy plus radiotherapy, nor adjuvant chemotherapy plus radiotherapy, have shown such consistent benefits as CRT in prolonging survival.[27,30–32] Nonetheless, two trials conducted in the 1990s suggested that neoadjuvant chemotherapy could improve survival[33,34] and reduce distant failure rates.[34] It is also now well documented that neoadjuvant treatment can be used to drive efficient therapeutic programs of organ preservation[35,36] without compromising overall survival.[35] Actually, neoadjuvant chemotherapy and CRT might play complementary roles: while the strengths of CRT lie more in enhancing locoregional control,[30] neoadjuvant chemotherapy appears more effective in minimising the risk of distant metastases.[30] A number of interesting studies have been published which describe attempts to improve survival by reducing the development of distant disease through intensive courses of neoadjuvant therapy followed by concomitant CRT.[37–40] In addition, a recent analysis of five phase II trials confirmed the different patterns of failure of two different 5-FU/hydroxyurea-based CRT strategies, one incorporating an intensive course of neoadjuvant chemotherapy.[41] In this analysis, intensive cisplatin/5-FU induction chemotherapy followed by split-course CRT led to a lower 5-year rate of distant failure (13% versus 22%, $p = 0.03$) but a higher 5-year rate of locoregional failure (31% versus 17%, $p = 0.01$) than intensified, split-course, hyperfractionated multi-agent CRT alone. Moreover, there was no significant difference in the 5-year progression-free (59% versus 62%) or overall (46% versus 48%) survival rates between the two treatment strategies. Interest in this avenue of research has been recently rekindled by the successful inclusion of taxanes in neoadjuvant regimens strongly suggests that the role of neoadjuvant chemotherapy should be revisited, including its use prior to CRT.[42–44]

5. CRT: efficacy versus toxicity

In the context of very aggressive combination regimens, the therapeutic benefit of CRT can be significantly jeopardised by undue toxicity, particularly regarding acute side effects.[45] Mucositis and xerostomia are common toxicities in patients undergoing radiotherapy and are seen with increased frequency with altered fractionation regimens. CRT is invariably associated with an increase in reports of these and other acute side effects,[46–48] and this can be exacerbated in altered fractionation-based regimens.[30] Patients receiving CRT also experience significant haematological toxicities.[16,17,19,47] Significant increases in severe (grade 3/4) acute toxicities are commonly reported, and data from a number of trials show increases in grade 3/4 mucositis of up to 32% and in any grade 3/4 toxicity of approximately 40%.[4,14,16,46,47] In some of these patients such toxicities can be very severe and even life-threatening.[49]

Although there is evidence of late toxicity developing in some CRT-treated patients,[4,50] whether this is a consequence of the addition of chemotherapy to radiotherapy is an open question. Huguenin et al. found that the incidence of late toxicity was comparable between the radiotherapy and cisplatin plus radiotherapy arms of their study, and in both groups the most frequent event (>20% in both arms) was permanent xerostomia and dysphagia.[18] Wendt et al. also reported no significant difference in the incidence of serious late effects between radiotherapy and radiotherapy/cisplatin/5-FU/FA.[4] Similarly, in another study, the overall incidence of late effects at 5-years post-treatment did not indicate a higher level of late toxicity in the CRT-treated patients compared with those receiving radiotherapy.[50] However, there were significant differences in favour of the radiotherapy-only group when the incidences in the most commonly damaged organs were compared (salivary glands, skin, teeth, mucosa and mandible).

Typically, many patients presenting with SCCHN have a poor performance status[51] and are not amenable to aggressive regimens of chemotherapy. Moreover, the maximum tolerable toxicity has probably been reached with the most

widely used chemotherapy regimens of bolus cisplatin (100 mg/m^{2}every 3 weeks): indeed, around only two-thirds of patients in clinical trials may receive the full number of cycles of chemotherapy to schedule as planned.[47,52] The problems with the delivery of optimal chemotherapy doses as part of CRT regimens will most likely be compounded outside the setting of a clinical trial.

6. The concept of biological cooperation: targeted agents

Considerable attention has been focused on the use of new anti-cancer drugs which have been engineered to interact with defined tumour-associated molecular targets. The fact that the specificity of such agents will be high by design has given rise to the expectation that targeted drugs will be very active but generally well-tolerated. The selective inhibition of tumour cell repopulation following radiotherapy, while at the same time leaving normal tissues unaffected, is one possible approach for optimising the therapeutic index.[45] Of interest in this context are agents targeting the epidermal growth factor receptor (EGFR), a member of an important family of transmembrane signalling proteins.[53] EGFR signalling is associated with control of normal cell growth and differentiation, as well as tumourigenesis and disease progression in malignant tissues.[54] EGFR is richly expressed by a wide variety of solid tumours, including SCCHN, in which nearly all lesions demonstrate EGFR expression on IHC (immunohistochemistry) analysis.[55] High levels of expression appear to be directly correlated with aggressive tumour growth and reduced survival.[56–58] EGFR is also known to mediate the resistance of cancer cells to radiation in a manner proportional to the degree of receptor expression.[59] The prognostic significance of high levels of expression[60,61] has emphasised the importance of EGFR as an anti-cancer drug target.[62,63]

Cetuximab is an IgG1 monoclonal antibody which specifically targets EGFR with high affinity and competitively inhibits its endogenous ligand binding. This action inhibits receptor signal transduction directly, by preventing the EGFR monomer from adopting the extended configuration necessary for dimerisation, and indirectly, by stimulating EGFR internalisation and degradation.[64] EGFR blockade leads to the inhibition of cellular proliferation, which is a reflection of arrest in the G1 phase of the cell cycle and/or an increase in apoptosis.[63] Ultimately, this may lead to a reduction in the metastatic potential of a tumour.[63,65,66]

In human xenograft models, the impact of cetuximab on growth inhibition is often more pronounced than in cell culture, indicating the likelihood of the involvement of additional anti-cancer mechanisms, such as the inhibition of angiogenesis.[63] Cetuximab has been shown to inhibit the production of vascular endothelial growth factor (VEGF) in epidermoid carcinoma cells, which causes a fall in the number of tumour blood vessels. Furthermore, it causes the down-regulation of interleukin (IL-8) and basic fibroblast growth factor (bFGF) expression, as well as the involution of tumour blood vessels and consequent inhibition of tumour growth.[67] The anti-metastatic potential of cetuximab has also been demonstrated in mice with 253J B-V[67] and human prostate tumours.[68] In addition, an ability to inhibit spontaneous metastasis in a severe combined immunodeficiency mouse xenograft model of metastatic melanoma, may be indicative of an antibody-dependent cellular cytotoxicity response.[69]

7. Pre-clinical activity of cetuximab

Tumour cells depend upon continued stimulation by growth factors.[65] Therefore, the inhibition of the EGFR-signalling pathway might provide an effective means of controlling tumour growth (Fig. 1). Indeed, *in vitro* and *in vivo* pre-clinical studies have shown the potential for cetuximab to modulate treatment outcome in SCCHN.[70] For example, it has been demonstrated that cetuximab enhances the anti-tumour effects of, or has its activity enhanced by, a variety of chemotherapeutic agents[65,71–75] and radiotherapy.[65,76–78] *In vitro* studies have demonstrated the ability of cetuximab to enhance the effects of radiation on human SCC tumour cell lines following blockade of the EGFR signalling cascade.[70,76,79] The ability of cetuximab to augment tumour radio response has also been established in SCC tumour xenografts in athymic mice.[70,80] Cetuximab is thought to exert its synergistic effects with radiotherapy at least in part by strong inhibition of radiation-induced DNA damage repair in tumour cells.[76] Pre-clinical studies using fractionated radiation have demonstrated cetuximab to improve local tumour control both by decreasing repopulation and increasing re-oxygenation.[81]

Based on these promising pre-clinical findings, it was a logical step to exploit the synergy between cetuximab and chemotherapy and radiotherapy and to investigate the effects of cetuximab in the clinical setting in the treatment of head and neck cancers.[63,82]

8. Cetuximab plus radiotherapy in the treatment of locally advanced SCCHN

Cetuximab showed encouraging activity in an initial study in patients with locally advanced SCCHN.[83] In this phase I trial, 16 patients with advanced SCCHN received treatment with cetuximab combined with either conventional (70 Gy, 2 Gy/day) or hyperfractionated (76.8 Gy, 1.2 Gy/twice daily) radiotherapy. There was an impressive 100% response rate, as all patients achieved a major objective response (13 complete and two partial responses) and interestingly, both treatments were generally well tolerated.

More recently, the results from a large, phase III, international, multicentre study to evaluate the combination of cetuximab with radiotherapy in locally advanced head and neck cancer patients ($n = 424$) have attracted a great deal of attention.[84] This trial, reported by Bonner et al., is the first large-scale study to investigate the efficacy of combining a targeted agent and radiotherapy in this patient group. The results showed that the addition of cetuximab to radiotherapy significantly improved locoregional control and survival compared with radiotherapy alone.

Patients were stratified by Karnofsky performance status ([KPS] 90%–100% versus 60%–80%), regional node involvement (positive versus negative), tumour stage (T1–3 versus T4) and radiation fractionation (concomitant boost versus once-daily versus twice-daily) and then randomised (1:1) to treatment

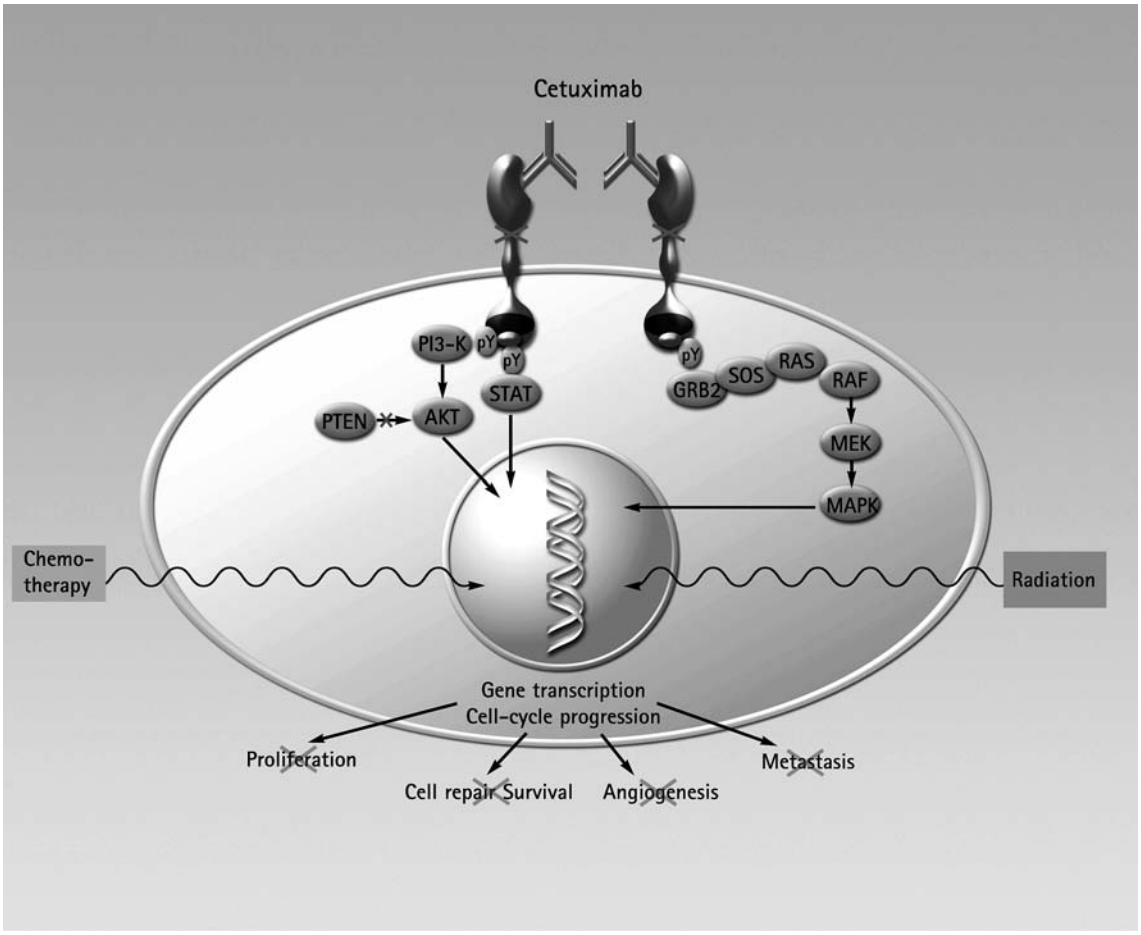

Fig. 1

with radiotherapy alone for 7–8 weeks ($n = 213$) or in combination with weekly-administered cetuximab ($n = 211$). The median age of patients in the radiotherapy and cetuximab plus radiotherapy groups was 58 and 56 years, respectively, and the majority were male. Most patients had a KPS of 90%–100%, and the majority presented with oropharyngeal tumours. The treatment arms were well balanced with regard to patient and treatment characteristics.

The addition of cetuximab to radiotherapy significantly improved survival and locoregional control (defined as the absence of locoregional disease progression at the scheduled follow-up visits) compared with radiotherapy alone (Table 1). Median overall survival with cetuximab plus radiotherapy was 49 months, almost 20 months longer than seen with radiotherapy alone (29.3 months, $p = 0.03$; log-rank test). Similarly, there was a clear advantage for cetuximab plus radiotherapy over radiotherapy alone in the 3-year survival rate (55% versus 45%, $p = 0.05$). Cetuximab plus radiotherapy was therefore associated with a 26% risk reduction in mortality compared with radiotherapy alone (hazard ratio, HR: 0.74). The median duration of locoregional control after treatment with cetuximab plus radiotherapy was 9.5 months longer than after radiotherapy alone (24.4 months versus 14.9 months, $p = 0.005$; log-rank test). There was also a clear

Table 1 – Efficacy results for phase III randomised study[84] comparing cetuximab plus radiotherapy with radiotherapy alone in patients with locally advanced SCCHN

	Radiotherapy alone ($n = 213$)	Cetuximab + radiotherapy ($n = 211$)	Hazard ratio [CI]/ p value
Median survival	29.3 months	49.0 months	0.74 [0.57–0.97] $p = 0.03$
3-year rate	45%	55%	$p = 0.05$
Median locoregional control	14.9 months	24.4 months	0.68 [0.52–0.89] $p = 0.005$
3-year rate	34%	47%	$p < 0.01$
Median progression-free survival	12.4 months	17.1 months	0.70 [0.54–0.90] $p = 0.006$
3-year rate	31%	42%	$p = 0.04$

CI = 95% confidence intervals.

advantage in the 3-year locoregional control rates ($p < 0.01$). Overall, cetuximab was associated with a 32% reduction in the risk of locoregional failure compared with radiotherapy alone (HR: 0.68). The results from this large study show that the addition of cetuximab to radiotherapy results in convincing, statistically significant and clinically meaningful improvements in locoregional control, overall survival and progression-free survival. The value and quality of the data are supported by the fact that locoregional control was assessed in a blinded fashion by an independent clinical review committee. Additionally it should be emphasised that with a population of more than 420 patients, the Bonner study[84] is one of the largest ever performed in this setting.

9. Safety profile of cetuximab plus radiotherapy

Cetuximab is well tolerated, the most common side effect being an acne-like rash (characteristic of EGFR inhibitors) which is generally mild to moderate (grade 1/2) in the majority of patients. Of particular relevance to its use in combination with radiotherapy (and/or chemotherapy) are the findings from clinical studies in colorectal cancer and SCCHN that cetuximab does not increase the side effects of chemotherapy or radiotherapy. These findings are supported by the data from the Bonner study, in which cetuximab did not statistically significantly increase the acute toxicities associated with radiotherapy, particularly: mucous membrane disorders, radiation dermatitis and dysphagia, which were seen in similar numbers of patients in each arm (Table 3). There was some additional toxicity that could be attributed to cetuximab, including grade 3–5 acne-like rash (17% versus 1%) and a relatively greater incidence of grade 3–5 infusion reactions (3% versus 0%).

10. Comparison of cetuximab plus radiotherapy with CRT

There are no randomised trials directly comparing cetuximab plus radiotherapy and CRT. However, to put the findings of the Bonner study into context with CRT, the results from the study can be viewed alongside those from a number of randomised studies (involving more than 100 patients/arm) comparing CRT with radiotherapy in locally advanced disease

Table 2 – Efficacy of radiotherapy alone or in combination with chemotherapy in published randomised studies on patients with locally advanced SCCHN in comparison with results from a phase III randomised study comparing cetuximab plus radiotherapy with radiotherapy[84]

Planned treatment		*n*	3-year rate (%)		Median OS time (months)	Δ Median OS time (months)
			LRC	Survival		
Conventional RT[16,85]						
RT	Total 70 Gy (7 weeks): 2 Gy/day for 5 days/week	113	42	31	[13]	7[85]
CRT	Same RT + carboplatin 70 mg/m^2/day + 5-FU 600 mg/m^2/day on days 1–4, 22–25, 43–46	109	66	51	[20]	
Hyperfractionated RT[18]						
RT	Total median dose 74.4 Gy (72–76.8 Gy): 1.2 Gy twice daily over 7 weeks	112	40	(50)	29	18
CRT	Same RT + cisplatin 20 mg/m^2/day for 5 days in weeks 1 + 5 (or 6)	112	56	(60)	47	
Hyperfractionated accelerated RT (concomitant boost)[86,87]						
RT	Total 69.9 Gy (38 days): 1.8 Gy/day weeks 1–3, 1.8 + 1.5 Gy/day weeks 4–5	127	38	(30)	[16]	7[87]
CRT	Same RT with carboplatin 70 mg/m^2/day + 5-FU 600 mg/m^2/day on days 1–5, 29–33	113	50	(40)	[23]	
RT[24]	Total 77.6 Gy (40 days): 14 Gy (2 Gy/day) then 1.4 Gy twice daily	194	39.2	28.6	16	7
CRT	Total RT 70.6 Gy (40 days): 30 Gy (2 Gy/day) then 1.4 Gy twice daily + mitomycin 10 mg/m^2 days 5 and 36 + 5-FU 600 mg/m^3 over days 1–5	190	51.8	37.5	23	
Accelerated RT with breaks[4]						
RT	Total 70.2 Gy (51 days): 1.8 Gy twice daily in three courses (23.4 Gy/course)	140	17	24	(16)	14
CRT	Same RT + cisplatin 60 mg/m^2 on days 2, 22, 44 and 5-FU 350 mg/m^2/day + FA 50 mg/m^2/day on days 2–5, 22–25, 44–47	130	35	49	(30)	
Cetuximab + radiotherapy[84]						
RT	6–7 weeks: once daily (70 Gy, 35 fractions), twice daily (72–76.8 Gy, 60–64 fractions), or concomitant boost (72 Gy, 42 fractions)	213	34	45	29.3	19.7
Cetux + RT	Same RT + cetuximab (1st dose 400 mg/m^2, 6 or 7 subsequent doses 250 mg/m^2/week)	211	47	55	49.0	

CRT = chemotherapy-enhanced radiation therapy; FA = folinic acid; 5-FU = 5-fluorouracil; LRC = locoregional control; OS = overall survival; RT = radiotherapy. Italic numbers in parentheses have been extracted from Kaplan–Meier curves.
*2-year rate.

Table 3 – Most common[a] grade 3–5 adverse events (% patients) occurring in patients receiving radiotherapy alone or in combination with cetuximab: results from a randomised phase III study[84]

COSTART preferred term	RT alone (n = 212)	Cetuximab + RT (n = 208)	p value
Mucositis	52	56	0.44
Dysphagia	30	26	0.45
Radiation dermatitis	18	23	0.27
Acne-like rash	1	17	<0.001
Weight loss	7	11	0.12
Dehydration	8	6	0.57
Pain	7	6	0.84
Anaemia	6	1	0.006
Constipation	5	5	1.00
Asthenia	5	4	0.64
Xerostomia	3	5	0.32

COSTART = Coding Symbols for Thesaurus of Adverse Reaction Terms; RT = radiotherapy.
a Occurring in at least 5% of patients in one treatment arm.

(Table 2[4,16,18,24,85–87]). Although such a comparison is limited by differences in methodology and inconsistent definitions of locoregional control/failure, a number of observations can be made.

In this comparison, the results for the radiotherapy arm of the Bonner study were generally better than those seen in the radiotherapy arms of the CRT studies. In all CRT studies, the median overall survival times for CRT were better than for the corresponding radiotherapy only groups. In addition, the median survival with cetuximab plus radiotherapy in the Bonner study (49 months) was in the region of the upper end of the range of median survivals seen with CRT (20–47 months), but was achieved without an increase in clinically significant toxicities. As direct comparisons of absolute survival values between studies is difficult, it is more meaningful to compare the increase in survival (or *survival time advantage*) within an individual study conferred by the administration of chemotherapy or cetuximab over radiotherapy alone (Δ median OS, Table 2, Fig. 2). The median survival time advantage for adding chemotherapy to radiotherapy, which ranged from 7 to 18 months, was lower than that achieved by adding cetuximab to radiotherapy (nearly 20 months). Cetuximab would therefore appear to be highly active in this setting while not significantly increasing the toxicities commonly associated with radiotherapy.

11. Cetuximab plus chemoradiotherapy

The combination of cetuximab and CRT is a logical development of strategies based on drug-radiotherapy interactions. In a study reported by Pfister et al., patients with locally advanced SCCHN received concomitant boost radiotherapy (70 Gy), together with cisplatin (100 mg/m^2 IV, weeks 1 and 4) and cetuximab (initial dose 400 mg/m^2, followed by subsequent doses of 250 mg/m^2/week).[88] Surgery was reserved for cases of relapse or persistent neck disease. A total of 22 patients, median age 57 years and median KPS of 90% (range 70%–90%), entered the study, the majority of the patients (86%) had stage IV disease. The overall response to this regimen was excellent: of 16 evaluable patients, 15 (94%) had an objective response (two complete and 13 partial responses). At a median follow-up of 52 months, 3-year progression-free and overall survival were 56% and 76%, respectively. The study was closed prematurely due to significant levels of tox-

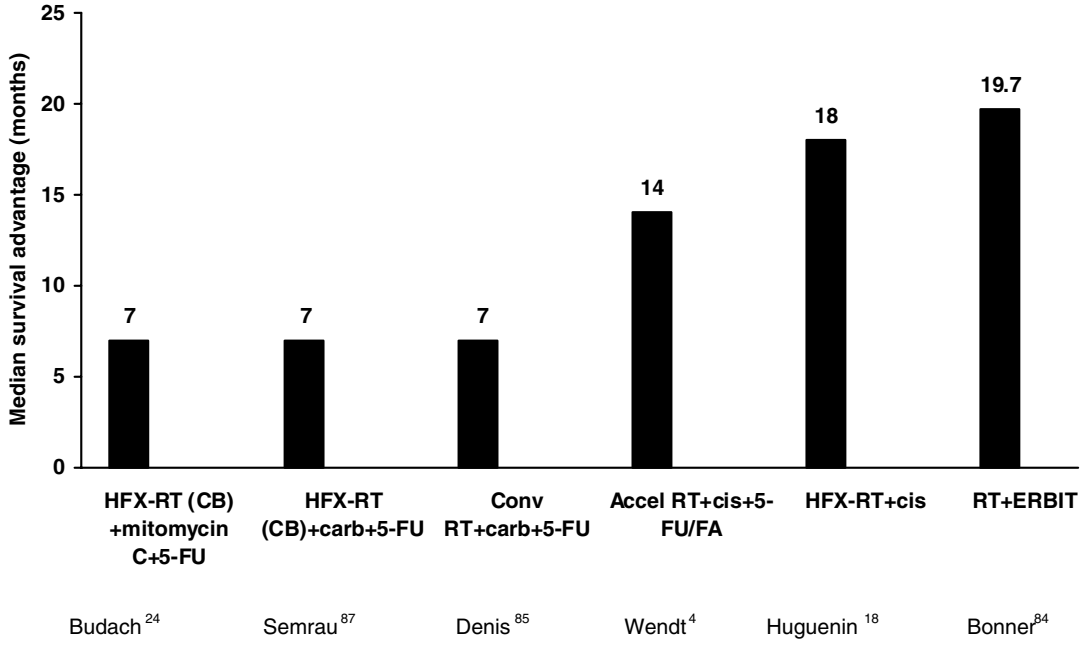

Fig. 2 – Cetuximab plus RT is associated with a higher survival advantage than CRT over RT. Data are taken from randomised studies involving over 100 patients/treatment arm. HFX-RT = hyperfractionated RT; CB = concomitant boost; carb = carboplatin; cis = cisplatin; conv = conventional; accel = accelerated. See text and Table 2 for details.

icity, although a relationship between this toxicity and any particular treatment was unclear.

12. Discussion and conclusions

When they are amenable to chemotherapy, CRT is nowadays considered the standard treatment for patients with locally advanced SCCHN. Nevertheless the increase in toxicity and poor compliance reported in studies with commonly used CRT regimens, usually based on the use of cisplatin 100 mg/m^2 every 3 weeks for three cycles, limits the implementation of this approach on a larger scale for this patient population. Optimisation of CRT strategies should therefore focus on the trade-off between treatment efficacy and tolerability to treatment, thereby improving patient quality of life. The addition of novel, biologically-oriented therapies to radiotherapy may prove instrumental in improving the outcome of patients with locally advanced SCCHN. Compared with radiotherapy alone, the combination of the EGFR inhibitor cetuximab and radiotherapy significantly improves locoregional control and overall survival in locally advanced disease.[84] In addition, albeit within the limitations of a comparison with historical data, the combination of cetuximab and radiotherapy appears to have efficacy benefits over radiotherapy at least as great as those seen with CRT, but without the associated toxicities.

The Bonner trial[84] undoubtedly paves the way for further prospective investigations that would confirm the efficacy of cetuximab, whatever the level of tumour resectability. Such studies should perhaps attempt to identify subgroups of patients with the highest response to cetuximab-containing regimens.

Obviously the use of non-cytotoxic drugs is still in its infancy and to optimise their clinical application we'll have to answer a number of questions first. In particular, should we focus on EGFR pathways or will we have to target both EGFR and VEGF mitogenic signals? Answering this question is bound to require time since the magnitude of the effects yielded by mono-or multi-targeted therapies markedly varies in function of the tumour site: for instance, results observed in patients with colorectal cancer can not be extrapolated to those presenting with head and neck carcinoma, and vice versa. Targeting other pathways in concomitance with cytotoxic drugs and/or radiation is another appealing approach. A number of genes allowing extensive communication between insulin-like growth factor-1 (IGF-1), p53, AKT, and mammalian target of rapamycin (mTOR) pathways have been identified. In turn the development of new agents designed to target various steps of c-Myc, Ras, and IGF cascade, as well as very recent advances in the identification of novel inhibitors as well as antisense oligonuleotides (ASOs) and siRNA will herald extensive clinical programs that will help investigators know more about the safety and effectiveness of non cytotoxic, targeted therapies, both as single agents or in combination with chemotherapy, radiation or CRT.

In conclusion, the combination of cetuximab and radiotherapy offers significant benefits over radiotherapy alone in the treatment of locally advanced SCCHN. This combination could represent the indication of choice in patients presenting with intermediate-risk disease, for whom the satisfactory locoregional control rates do not justify the use of toxic CRT regimens. In patients with high- or very high-risk SCCHN, not amenable to chemotherapy or likely to show poor treatment compliance, this combination may also provide an effective and well tolerated alternative to CRT.

Finally the addition of cetuximab to CRT is certainly worth investigating in patients with locally advanced disease, as adjuvant treatment, in the framework of organ preservation programs, and when the tumour is unresectable.

Conflict of interest statement

None declared.

REFERENCES

1. Parkin DM, Bray F, Ferlay J, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;**55**(2):74–108.
2. Schantz SP, Harrison LB, Forastiere A. Tumors of the nasal cavity and paranasal sinuses, nasopharynx, oral cavity, and oropharynx. In: DeVita VT, Hellman SA, Rosenberg SA, editors. *Cancer. Principles and practice of oncology*. 6th ed. Philadelphia: Lippincott Williams & Wilkins; 2001. p. 797–860.
3. Adelstein DJ, Saxton JP, Lavertu P, et al. A phase III randomized trial comparing concurrent chemotherapy and radiotherapy with radiotherapy alone in resectable stage III and IV squamous cell head and neck cancer: preliminary results. *Head Neck* 1997;**19**(7):567–75.
4. Wendt TG, Grabenbauer GG, Rodel CM, et al. Simultaneous radiochemotherapy versus radiotherapy alone in advanced head and neck cancer: a randomized multicenter study. *J Clin Oncol* 1998;**16**(4):1318–24.
5. Lamont EB, Vokes EE. Chemotherapy in the management of squamous-cell carcinoma of the head and neck. *Lancet Oncol* 2001;**2**(5):261–9.
6. Lefebvre JL. Current clinical outcomes demand new treatment options for SCCHN. *Ann Oncol* 2005;**16**(Suppl 16):vi7–vi12.
7. Taylor SG, Murthy AK, Vannetzel JM, et al. Randomized comparison of neoadjuvant cisplatin and fluorouracil infusion followed by radiation versus concomitant treatment in advanced head and neck cancer. *J Clin Oncol* 1994;**12**(2):385–95.
8. Horiot JC, Le Fur R, N'Guyen T, et al. Hyperfractionation versus conventional fractionation in oropharyngeal carcinoma: final analysis of a randomized trial of the EORTC cooperative group of radiotherapy. *Radiother Oncol* 1992;**25**(4):231–41.
9. Horiot JC, Bontemps P, van den Bogaert W, et al. Accelerated fractionation (AF) compared to conventional fractionation (CF) improves loco-regional control in the radiotherapy of advanced head and neck cancers: results of the EORTC 22851 randomized trial. *Radiother Oncol* 1997;**44**(2):111–21.
10. Fu KK, Pajak TF, Trotti A, et al. A Radiation Therapy Oncology Group (RTOG) phase III randomized study to compare hyperfractionation and two variants of accelerated fractionation to standard fractionation radiotherapy for head and neck squamous cell carcinomas: first report of RTOG 9003. *Int J Radiat Oncol Biol Phys* 2000;**48**(1):7–16.
11. Browman GP, Hodson DI, Mackenzie RJ, Bestic N, Zuraw L. Choosing a concomitant chemotherapy and radiotherapy regimen for squamous cell head and neck cancer: A systematic review of the published literature with subgroup analysis. *Head Neck* 2001;**23**(7):579–89.

12. Bernier J, Cooper JS. Chemoradiation after surgery for high-risk head and neck cancer patients: how strong is the evidence? *Oncologist* 2005;**10**(3):215–24.
13. Cooper JS, Ang KK. Concomitant chemotherapy and radiation therapy certainly improves local control. *Int J Radiat Oncol Biol Phys* 2005;**61**(1):7–9.
14. Adelstein DJ, Li Y, Adams GL, et al. An intergroup phase III comparison of standard radiation therapy and two schedules of concurrent chemoradiotherapy in patients with unresectable squamous cell head and neck cancer. *J Clin Oncol* 2003;**21**(1):92–8.
15. Brizel DM, Albers ME, Fisher SR, et al. Hyperfractionated irradiation with or without concurrent chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 1998;**338**(25):1798–804.
16. Calais G, Alfonsi M, Bardet E, et al. Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *J Natl Cancer Inst* 1999;**91**(24):2081–6.
17. Jeremic B, Shibamoto Y, Milicic B, et al. Hyperfractionated radiation therapy with or without concurrent low-dose daily cisplatin in locally advanced squamous cell carcinoma of the head and neck: a prospective randomized trial. *J Clin Oncol* 2000;**18**(7):1458–64.
18. Huguenin P, Beer KT, Allal A, et al. Concomitant cisplatin significantly improves locoregional control in advanced head and neck cancers treated with hyperfractionated radiotherapy. *J Clin Oncol* 2004;**22**(23):4665–73.
19. Fountzilas G, Ciuleanu E, Dafni U, et al. Concomitant radiochemotherapy vs radiotherapy alone in patients with head and neck cancer: a Hellenic Cooperative Oncology Group Phase III Study. *Med Oncol* 2004;**21**(2):95–107.
20. Bensadoun RJ, Dassonville O, Ramaioli A, et al. Phase III multicenter randomized study of concurrent twice-a-day radiotherapy with and without cisplatin (BiCRF) in unresectable pharyngeal carcinoma. Results at 18 months (FNCLCC-GORTEC). *J Clin Oncol, ASCO Annual Meeting Proceedings (Post-Meeting Edition)* 2004;**22**, **No 14S**:Abstract 5504.
21. Maguire PD, Meyerson MB, Neal CR, et al. Toxic cure: Hyperfractionated radiotherapy with concurrent cisplatin and fluorouracil for Stage III and IVA head-and-neck cancer in the community. *Int J Radiat Oncol Biol Phys* 2004;**58**(3):698–704.
22. Merlano M, Benasso M, Corvo R, et al. Five-year update of a randomized trial of alternating radiotherapy and chemotherapy compared with radiotherapy alone in treatment of unresectable squamous cell carcinoma of the head and neck. *J Natl Cancer Inst* 1996;**88**(9):583–9.
23. Pajak TF, Laramore GE, Marcial VA, et al. Elapsed treatment days–a critical item for radiotherapy quality control review in head and neck trials: RTOG report. *Int J Radiat Oncol Biol Phys* 1991;**20**(1):13–20.
24. Budach V, Stuschke M, Budach W, et al. Hyperfractionated accelerated chemoradiation with concurrent fluorouracil-mitomycin is more effective than dose-escalated hyperfractionated accelerated radiation therapy alone in locally advanced head and neck cancer: final results of the radiotherapy cooperative clinical trials group of the German Cancer Society 95-06 Prospective Randomized Trial. *J Clin Oncol* 2005;**23**(6):1125–35.
25. Chan AT, Leung SF, Ngan RK, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst* 2005;**97**(7):536–9.
26. Bourhis J, Armand C, Pignon JP. Update of MACH-NC (Meta-Analysis of Chemotherapy in Head & Neck Cancer) database focused on concomitant chemoradiotherapy. *J Clin Oncol, ASCO Annual Meeting Proceedings (Post-Meeting Edition)* 2004;**22**,(No 14S):Abstract 5505.
27. Pignon JP, Bourhis J, Domenge C, Designe L. Chemotherapy added to locoregional treatment for head and neck squamous-cell carcinoma: three meta-analyses of updated individual data. MACH-NC Collaborative Group. Meta-Analysis of Chemotherapy on Head and Neck Cancer. *Lancet* 2000;**355**(9208):949–55.
28. Jeremic B, Milicic B, Dagovic A, Vaskovic Z, Tadic L. Radiation therapy with or without concurrent low-dose daily chemotherapy in locally advanced, nonmetastatic squamous cell carcinoma of the head and neck. *J Clin Oncol* 2004;**22**(17):3540–8.
29. Bernier J. Alteration of radiotherapy fractionation and concurrent chemotherapy: a new frontier in head and neck oncology? *Nature Clinical Practice Oncology* 2005;**2**(6):305–14.
30. Cohen EE, Lingen MW, Vokes EE. The expanding role of systemic therapy in head and neck cancer. *J Clin Oncol* 2004;**22**:1743–52.
31. Browman GP. Evidence-based recommendations against neoadjuvant chemotherapy for routine management of patients with squamous cell head and neck cancer. *Cancer Invest* 1994;**12**(6):662–70.
32. Stell PM, Rawson NS. Adjuvant chemotherapy in head and neck cancer. *Br J Cancer* 1990;**61**(5):779–87.
33. Domenge C, Hill C, Lefebvre JL, et al. Randomized trial of neoadjuvant chemotherapy in oropharyngeal carcinoma. French Groupe d'Etude des Tumeurs de la Tete et du Cou (GETTEC). *Br J Cancer* 2000;**83**(12):1594–8.
34. Paccagnella A, Orlando A, Marchiori C, et al. Phase III trial of initial chemotherapy in stage III or IV head and neck cancers: a study by the Gruppo di Studio sui Tumori della Testa e del Collo. *J Natl Cancer Inst* 1994;**86**(4):265–72.
35. The Department of Veterans Affairs Laryngeal Cancer Study Group. Induction chemotherapy plus radiation compared with surgery plus radiation in patients with advanced laryngeal cancer. *N Engl J Med* 1991;**324**(24):1685-90.
36. 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.
37. Machtay M, Rosenthal DI, Hershock D, et al. Organ preservation therapy using induction plus concurrent chemoradiation for advanced resectable oropharyngeal carcinoma: a University of Pennsylvania Phase II Trial. *J Clin Oncol* 2002;**20**(19):3964–71.
38. Vokes EE, Stenson K, Rosen FR, et al. Weekly carboplatin and paclitaxel followed by concomitant paclitaxel, fluorouracil, and hydroxyurea chemoradiotherapy: curative and organ-preserving therapy for advanced head and neck cancer. *J Clin Oncol* 2003;**21**(2):320–6.
39. Haraf DJ, Rosen FR, Stenson K, et al. Induction chemotherapy followed by concomitant TFHX chemoradiotherapy with reduced dose radiation in advanced head and neck cancer. *Clin Cancer Res* 2003;**9**(16 Pt 1):5936–43.
40. Vokes EE, Kies M, Haraf DJ, et al. Induction chemotherapy followed by concomitant chemoradiotherapy for advanced head and neck cancer: impact on the natural history of the disease. *J Clin Oncol* 1995;**13**(4):876–83.
41. Brockstein B, Haraf DJ, Rademaker AW, et al. Patterns of failure, prognostic factors and survival in locoregionally advanced head and neck cancer treated with concomitant chemoradiotherapy: a 9-year, 337-patient, multi-institutional experience. *Ann Oncol* 2004;**15**(8):1179–86.
42. Pignon JP, Syz N, Posner M, et al. Adjusting for patient selection suggests the addition of docetaxel to 5-fluorouracil-

cisplatin induction therapy may offer survival benefit in squamous cell cancer of the head and neck. *Anticancer Drugs* 2004;**15**(4):331–40.
43. Hainsworth JD, Meluch AA, McClurkan S, et al. Induction paclitaxel, carboplatin, and infusional 5-FU followed by concurrent radiation therapy and weekly paclitaxel/carboplatin in the treatment of locally advanced head and neck cancer: a phase II trial of the Minnie Pearl Cancer Research Network. *Cancer J* 2002;**8**(4):311–21.
44. Vermorken JB, Remenar E, Van Herpen C, et al. Standard cisplatin/infusional 5-fluorouracil (PF) vs docetaxel (T) plus PF (TPF) as neoadjuvant chemotherapy for nonresectable locally advanced squamous cell carcinoma of the head and neck (LA-SCCHN): A phase III trial fo the EORTC Head and Neck Cancer Group (EORTC #24971). *J Clin Oncol, ASCO Annual Meeting Proceedings (Post-Meeting Edition)* 2004;**22**, No 14S:Abstract 5508.
45. Bernier J, Bentzen SM. Altered fractionation and combined radio-chemotherapy approaches: pioneering new opportunities in head and neck oncology. *Eur J Cancer* 2003;**39**(5):560–71.
46. Cooper JS, Pajak TF, Forastiere AA, et al. Postoperative concurrent radiotherapy and chemotherapy for high-risk squamous-cell carcinoma of the head and neck. *N Engl J Med* 2004;**350**(19):1937–44.
47. Bernier J, Domenge C, Ozsahin M, et al. Postoperative irradiation with or without concomitant chemotherapy for locally advanced head and neck cancer. *N Engl J Med* 2004;**350**(19):1945–52.
48. Bieri S, Bentzen SM, Huguenin P, et al. Early morbidity after radiotherapy with or without chemotherapy in advanced head and neck cancer. Experience from four nonrandomized studies. *Strahlenther Onkol* 2003;**179**(6):390–5.
49. Nguyen NP, Moltz CC, Frank C, et al. Dysphagia following chemoradiation for locally advanced head and neck cancer. *Ann Oncol* 2004;**15**(3):383–8.
50. Denis F, Garaud P, Bardet E, et al. Late toxicity results of the GORTEC 94-01 randomized trial comparing radiotherapy with concomitant radiochemotherapy for advanced-stage oropharynx carcinoma: comparison of LENT/SOMA, RTOG/EORTC, and NCI-CTC scoring systems. *Int J Radiat Oncol Biol Phys* 2003;**55**(1):93–8.
51. Kowalski LP, Carvalho AL. Natural history of untreated head and neck cancer. *Eur J Cancer* 2000;**36**(8):1032–7.
52. Al-Sarraf M, Pajak TF, Marcial VA, et al. Concurrent radiotherapy and chemotherapy with cisplatin in inoperable squamous cell carcinoma of the head and neck. An RTOG Study. *Cancer* 1987;**59**(2):259–65.
53. Ciardiello F, Tortora G. Anti-epidermal growth factor receptor drugs in cancer therapy. *Expert Opin Investig Drugs* 2002;**11**(6):755–68.
54. Arteaga C. Targeting HER1/EGFR: a molecular approach to cancer therapy. *Semin Oncol* 2003;**30**(3 Suppl 7):3–14.
55. Grandis JR, Melhem MF, Barnes EL, Tweardy DJ. Quantitative immunohistochemical analysis of transforming growth factor-alpha and epidermal growth factor receptor in patients with squamous cell carcinoma of the head and neck. *Cancer* 1996;**78**(6):1284–92.
56. Ang KK, Berkey BA, Tu X, et al. Impact of epidermal growth factor receptor expression on survival and pattern of relapse in patients with advanced head and neck carcinoma. *Cancer Res* 2002;**62**(24):7350–6.
57. Hitt R, Castellano D, Ciruelos E, et al. Overexpression of epidermal growth factor receptor (EGFR) and p53 mutations levels as prognostic factors in patients with locally-advanced head and neck cancer (LAHNC) treated with induction chemotherapy. *Proc Am Soc Clin Oncol* 2002;**22**:Abstract 972.
58. Magne N, Pivot X, Bensadoun RJ, et al. The relationship of epidermal growth factor receptor levels to the prognosis of unresectable pharyngeal cancer patients treated by chemo-radiotherapy. *Eur J Cancer* 2001;**37**(17):2169–77.
59. Liang K, Ang KK, Milas L, Hunter N, Fan Z. The epidermal growth factor receptor mediates radioresistance. *Int J Radiat Oncol Biol Phys* 2003;**57**(1):246–54.
60. Rubin Grandis J, Melhem MF, Gooding WE, et al. Levels of TGF-alpha and EGFR protein in head and neck squamous cell carcinoma and patient survival. *J Natl Cancer Inst* 1998;**90**(11):824–32.
61. Maurizi M, Almadori G, Ferrandina G, et al. Prognostic significance of epidermal growth factor receptor in laryngeal squamous cell carcinoma. *Br J Cancer* 1996;**74**(8):1253–7.
62. Huang SM, Harari PM. Epidermal growth factor receptor inhibition in cancer therapy: biology, rationale and preliminary clinical results. *Invest New Drugs* 1999;**17**(3):259–69.
63. Harari PM. Epidermal growth factor receptor inhibition strategies in oncology. *Endocr Relat Cancer* 2004;**11**(4):689–708.
64. Li S, Schmitz KR, Jeffrey PD, Wiltzius JJ, Kussie P, Ferguson KM. Structural basis for inhibition of the epidermal growth factor receptor by cetuximab. *Cancer Cell* 2005;**7**(4):301–11.
65. Laskin JJ, Sandler AB. Epidermal growth factor receptor: a promising target in solid tumours. *Cancer Treat Rev* 2004;**30**(1):1–17.
66. Herbst RS, Shin DM. Monoclonal antibodies to target epidermal growth factor receptor- positive tumors: a new paradigm for cancer therapy. *Cancer* 2002;**94**(5):1593–611.
67. Perrotte P, Matsumoto T, Inoue K, et al. Anti-epidermal growth factor receptor antibody C225 inhibits angiogenesis in human transitional cell carcinoma growing orthotopically in nude mice. *Clin Cancer Res* 1999;**5**(2):257–65.
68. Karashima T, Sweeney P, Slaton JW, et al. Inhibition of angiogenesis by the antiepidermal growth factor receptor antibody ImClone C225 in androgen-independent prostate cancer growing orthotopically in nude mice. *Clin Cancer Res* 2002;**8**(5):1253–64.
69. Naramura M, Gillies SD, Mendelsohn J, Reisfeld RA, Mueller BM. Therapeutic potential of chimeric and murine anti-(epidermal growth factor receptor) antibodies in a metastasis model for human melanoma. *Cancer Immunol Immunother* 1993;**37**(5):343–9.
70. Harari PM, Huang SM. Head and neck cancer as a clinical model for molecular targeting of therapy: combining EGFR blockade with radiation. *Int J Radiat Oncol Biol Phys* 2001;**49**(2):427–33.
71. Baselga J, Norton L, Masui H, et al. Antitumor effects of doxorubicin in combination with anti-epidermal growth factor receptor monoclonal antibodies. *J Natl Cancer Inst* 1993;**85**(16):1327–33.
72. Fan Z, Baselga J, Masui H, Mendelsohn J. Antitumor effect of anti-epidermal growth factor receptor monoclonal antibodies plus cis-diamminedichloroplatinum on well established A431 cell xenografts. *Cancer Res* 1993;**53**(19):4637–42.
73. Inoue K, Slaton JW, Perrotte P, et al. Paclitaxel enhances the effects of the anti-epidermal growth factor receptor monoclonal antibody ImClone C225 in mice with metastatic human bladder transitional cell carcinoma. *Clin Cancer Res* 2000;**6**(12):4874–84.
74. Bruns CJ, Harbison MT, Davis DW, et al. Epidermal growth factor receptor blockade with C225 plus gemcitabine results in regression of human pancreatic carcinoma growing orthotopically in nude mice by antiangiogenic mechanisms. *Clin Cancer Res* 2000;**6**(5):1936–48.
75. Prewett MC, Hooper AT, Bassi R, Ellis LM, Waksal HW, Hicklin DJ. Enhanced antitumor activity of anti-epidermal growth factor receptor monoclonal antibody IMC-C225 in

combination with irinotecan (CPT-11) against human colorectal tumor xenografts. *Clin Cancer Res* 2002;**8**(5):994–1003.
76. Huang SM, Harari PM. Modulation of radiation response after epidermal growth factor receptor blockade in squamous cell carcinomas: inhibition of damage repair, cell cycle kinetics, and tumor angiogenesis. *Clin Cancer Res* 2000;**6**(6):2166–74.
77. Bonner JA, Raisch KP, Trummell HQ, et al. Enhanced apoptosis with combination C225/radiation treatment serves as the impetus for clinical investigation in head and neck cancers. *J Clin Oncol* 2000;**18**(21 Suppl):47S–53S.
78. Nasu S, Ang KK, Fan Z, Milas L. C225 antiepidermal growth factor receptor antibody enhances tumor radiocurability. *Int J Radiat Oncol Biol Phys* 2001;**51**(2):474–7.
79. Huang SM, Bock JM, Harari PM. Epidermal growth factor receptor blockade with C225 modulates proliferation, apoptosis, and radiosensitivity in squamous cell carcinomas of the head and neck. *Cancer Res* 1999;**59**(8):1935–40.
80. Milas L, Mason K, Hunter N, et al. In vivo enhancement of tumor radioresponse by C225 antiepidermal growth factor receptor antibody. *Clin Cancer Res* 2000;**6**(2):701–8.
81. Krause M, Ostermann G, Petersen C, et al. Decreased repopulation as well as increased reoxygenation contribute to the improvement in local control after targeting of the EGFR by C225 during fractionated irradiation. *Radiother Oncol* 2005;**76**(2):162–7.
82. Harari PM, Huang SM. Combining EGFR inhibitors with radiation or chemotherapy: will preclinical studies predict clinical results? *Int J Radiat Oncol Biol Phys* 2004;**58**(3):976–83.
83. Robert F, Ezekiel MP, Spencer SA, et al. Phase I study of anti-epidermal growth factor receptor antibody cetuximab in combination with radiation therapy in patients with advanced head and neck cancer. *J Clin Oncol* 2001;**19**(13):3234–43.
84. Bonner JA, Harari P, Giralt J, et al. Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 2006;**354**(6):567–78.
85. Denis F, Garaud P, Bardet E, et al. Final results of the 94-01 French Head and Neck Oncology and Radiotherapy Group randomized trial comparing radiotherapy alone with concomitant radiochemotherapy in advanced-stage oropharynx carcinoma. *J Clin Oncol* 2004;**22**(1):69–76.
86. Staar S, Rudat V, Stuetzer H, et al. Intensified hyperfractionated accelerated radiotherapy limits the additional benefit of simultaneous chemotherapy–results of a multicentric randomized German trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2001;**50**(5):1161–71.
87. Semrau R, Mueller RP, Stuetzer H, et al. Efficacy of intensified hyperfractionated and accelerated radiotherapy and concurrent chemotherapy with carboplatin and 5-fluorouracil: Updated results of a randomized multicentric trial in advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 2006.
88. Pfister DG, Su YB, Kraus DH, et al. Concurrent cetuximab, cisplatin, and concomitant boost radiotherapy for locoregionally advanced, squamous cell head and neck cancer: a pilot phase II study of a new combined-modality paradigm. *J Clin Oncol* 2006;**24**(7):1072–8.