

Retrospective evaluation of concomitant cetuximab and radiotherapy tolerance for locoregional advanced head and neck squamous cell carcinoma treatment in patients unfit for platinum-based chemotherapy

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Abstract Radiotherapy associated with cetuximab (Cet-RT) is an alternative treatment to platinum-based chemoradiotherapy in locally advanced head and neck carcinoma (LAHNC). Reviews suggest that the use of cetuximab is associated with poorer tolerance in patients unfit for chemotherapy than in pivotal trial. We retrospectively studied patients first treated by Cet-RT for LAHNC presenting contraindications to chemoradiotherapy. Objectives were treated population description, acute tolerance, progression-free survival (PFS), overall survival (OS), and 3-month clinical response. Eighty-eight patients were included. Treatment was completed without delay for 43 patients. Grade 3–4 acute toxicity was described in 44.3%: mucositis ($n=20$), radiodermatitis ($n=25$) folliculitis ($n=10$), and anaphylaxis ($n=6$). Fourteen patients died during treatment. Median PFS and OS were 6.3 and 18.7 months, respectively. We confirm that Cet-RT tolerance in unfit patients is poorer than that in trials. Survival data illustrate patients' frailty and suggest that balanced use of Cet-RT is required in this population.

Introduction

The publication of Calais [1] and later on the updated MACH-NC meta-analysis [2] showed strong evidence that concomitant chemoradiotherapy is the standard of care of locally advanced head and neck squamous cell carcinoma (HNSCC). On the other hand, in 2006, Bonner et al. [3] demonstrated in a randomized study using cetuximab, a monoclonal antibody against the epidermal growth factor receptor increasing cell apoptosis in vitro, that concomitant radiotherapy plus cetuximab (Cet-RT) was able to improve locoregional control. In Bonner's study [4], Cet-RT was compared to radiotherapy alone, showing a gain of 10 months in local control without increasing toxicity in good general condition population. These two treatments share the same indications and determining when to use one or the other remains an open question.

A latest prospective phase II study [5] comparing Cet-RT to CT-RT (weekly cisplatin monotherapy) has unfortunately been discontinued because of slow accrual enrollment. Results showed an increased acute toxicity in Cet-RT but with similar efficacy among 70 included patients. Retrospective review [6] and retrospective trial [7] suggested that overall survival and progression-free survival would be significantly better in CT-RT group. HPV status does not seem to get involved in response to Cet-RT [8].

As it has been used for decades, CT-RT is usually kept as the first intention treatment; but whenever the patient presents contraindication to CT-RT, Cet-RT seems to be an interesting alternative in these locally advanced tumors. This explains the reason why patients receiving Cet-RT usually do show more comorbidities and a poorer general condition [9]. Patients unfit for concomitant chemotherapy might not benefit from Cet-RT as compared to Bonner prospective trial. We evaluated Cet-RT-treated population

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characteristics and tolerance with a local review, in order to see if treatment administration is acceptable.

Methods

Objectives

We first aimed to describe treated population (sex, age, reasons why platinum-based chemotherapy was contraindicated, general statement, and nutritional status), Cet-RT acute tolerance (weight loss, hospitalization, mucositis, epidermitis, folliculitis, and anaphylaxis), and treatment compliance. Our secondary goal was to evaluate if some particular patient characteristics were associated with higher toxicity rate and to describe 3-month clinical response.

Population

We retrospectively studied all patients treated by Cet-RT in our Comprehensive Cancer Centre (Centre Francois Baclesse, Caen, France) from October 2007 to November 2015.

Eligibility criteria were as follows: patients treated by Cet-RT, for a locally advanced head and neck squamous cell carcinoma (stage III and IV), with clinical contraindication to platinum-based chemotherapy, who received at least one cetuximab infusion.

Exclusion criteria were as follows: administration of an induction chemotherapy and previous neck irradiation.

Patients who interrupted cetuximab infusions due to anaphylactic reaction and those who died during treatment were excluded from acute cutaneous and mucosal toxicity evaluation.

In accordance with French law, formal approval from an ethics committee is not required for a single-institution retrospective study, nor a formal oral or written consent, but patients received explicit information indicating that their data could be used for research purpose at the time of their first medical consultation in our cancer center. None of them expressed written opposition. Declaration of clinical research has been done to the CNIL (French independent authority regulating personal data) (Declaration No. 2002152).

Treatment and assessment

Treatment schedule includes high-dose radiation therapy: 2 Gy per day, 5 days a week, up to 70 Gy in invaded areas and 50–56 Gy in uninvolved areas in 7 weeks. Radiotherapy technique was 3D conformal using association of photon and electron beams from 2007 to late 2013, and since 2011, intensity modulated with simultaneous integrated

boost, by means of helical or arc techniques with 6MV photon beams. Patients receive a loading dose of cetuximab (400 mg/m²) the week before the start of radiotherapy, then 250/mg² weekly. Data were collected retrospectively from medical assessment in computerized medical record. Acute toxicity was assessed according to Acute Radiation Morbidity Scoring Criteria (Radiation Therapy Oncology Group) for in-field dermatitis and mucositis and Common Terminology Criteria for Adverse Events (CTCAE) for out-field folliculitis.

Statistical analysis

The proportion of grade 3 or more toxicity was compared according to several factors using a Chi-squared test for qualitative variables (or Fisher exact test if needed) or a Student's *t* test for the quantitative age variable. Identically, the proportion of 3-month objective clinical response was compared according to several factors with the same statistical tests.

Progression-Free Survival (PFS) and Overall Survival (OS) were assessed using the Kaplan–Meier estimator and compared using a log-rank test between patients who experienced grade 3 or more toxicity and those who did not.

A *P* value < 0.05 was considered to denote significance.

Results

Population

Of the 131 patients who underwent radiotherapy associated with cetuximab in our center, 43 were excluded: 29 did not present any contraindication to platinum-based chemotherapy, 12 had a stage I or II disease, and 2 had a past neck irradiation. Eighty-eight patients were eligible for analysis (Figure 1). Patients ranged from 35 to 80 years old. 74 were men (sex ratio 5.3). Locations of primary tumor(s) were oral cavity (*n*=8), oropharynx (*n*=51), hypopharynx (*n*=13), and larynx (*n*=13). Multiple primary lesions were found in 2 patients. One patient had cervical nodes of unknown primary site. The main reasons contraindicating chemotherapy were cardiac diseases (*n*=25, 28.4%) and poor general condition (*n*=23, 26.1%). Other causes are detailed in Table 1. It is noteworthy that 16 patients suffered from multiple comorbidities.

Ninety-five percent of patients were active or past smokers, 76% were active or past drinkers. Social isolation was described in 39.8% of cases. Undernourishment was severe (defined by a BMI below 17 or a weight loss over 10% of total body weight) for *n*=42 and moderate (defined by a BMI between 17 and 18.5 or a weight loss from 5 to 10% of total body weight) for *n*=14 (Table 2).

Treatment compliance

Planned treatment, including 70 Gy radiotherapy and a total of 8 cetuximab injections, was completed without any delay for 43 patients (48.9%).

Irradiation was suspended for more than 3 days in 19 cases (10 days or more for 12 of them, up to 21 days) and definitively stopped in 6. Reasons for definitive radiotherapy interruption were bad general condition ($n=2$), skin

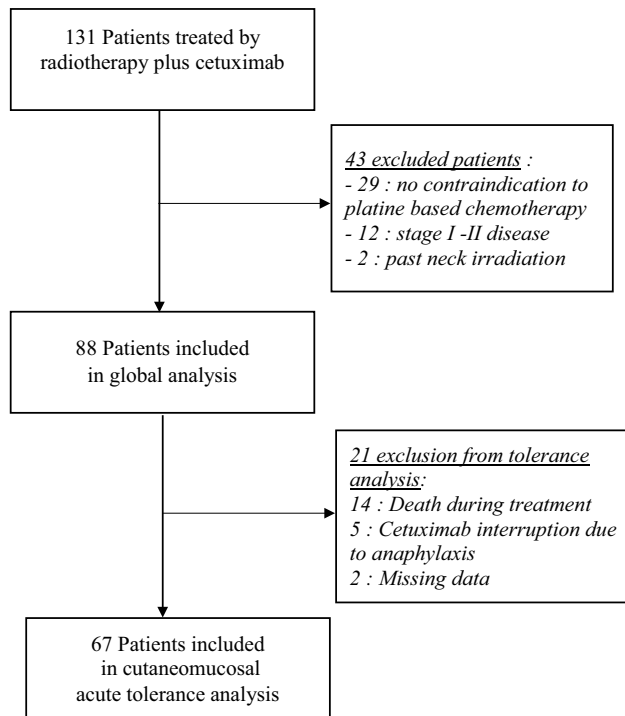


Fig. 1 Flow-chart

Table 1 Comorbidities contraindicating platinum-based chemoradiotherapy

Comorbidity	No (%)
Cardiac past history	25 (28.4)
Poor general condition	23 (26.1)
Expected compliance difficulties	9 (10.2)
Renal failure	8 (9.1)
Other active cancer	8 (9.1)
Vascular past history	7 (8.0)
Age	6 (6.8)
Respiratory past history	6 (6.8)
Liver failure (cirrhosis)	6 (6.8)
Neuropathy	3 (3.4)
Previous chemotherapy with poor tolerance	2 (2.3)
Thrombocytopenia	1 (1.1)
Hypoacusia	1 (1.1)

Table 2 Patient characteristics—no (%)

Sex	
Male	74 (84.1)
Female	14 (15.9)
Localisation	
Oral cavity	8 (9.1)
Oropharynx	51 (58.0)
Hypopharynx	13 (14.8)
Larynx	13 (14.8)
Multiple localisation	2 (2.3)
Node without primitive	1 (1.1)
Stage	
III	22 (26.2)
IVa	50 (59.5)
IVb	12 (14.3)
Social isolation	
Yes	33 (39.8)
No	50 (60.2)
Smoking	
Active	59 (67.8)
Past	24 (27.6)
None	4 (4.6)
Drinking	
Active	46 (54.1)
Past	19 (22.4)
None	20 (23.5)
Performance status (OMS)	
0	6 (6.9)
1	49 (56.3)
2	26 (29.9)
3	6 (7)
Undernourishment	
Severe	42 (47.7)
Moderate	14 (15.9)
None	32 (36.4)

toxicity ($n=2$), and dyspnea preventing from lying down ($n=2$). Reasons for temporary radiation suspension were in-field dermatitis ($n=13$), severe mucositis ($n=3$), and patient refusal of treatment ($n=1$).

Cetuximab was temporarily suspended in 4 patients due to skin toxicity and definitively stopped in 16 patients. Reasons for discontinuing cetuximab were skin toxicity ($n=10$) and grade 2 ($n=4$) or grade 4 ($n=2$) hypersensitivity reaction. Median number of administrated cycles before interruption due to skin toxicity was 5.5. One patient stopped both cetuximab and radiotherapy due to grade 3 epidermitis.

Death occurred during treatment in 14 cases (15.9%). Death etiologies were massive carotid hemorrhage ($n=2$), progressive disease ($n=2$), severe sepsis ($n=2$),

Table 3 Acute toxicities—no (%)

	None	Grade 1	Grade 2	Grade 3	Grade 4
Mucositis	1 (1.5)	10 (14.9)	36 (53.7)	19 (28.4)	1 (1.5)
In-field epidermitis	0 (0)	11 (16.4)	31 (46.3)	20 (29.9)	5 (7.5)
Out-field folliculitis	11 (16.7)	25 (37.9)	20 (30.3)	10 (15.2)	0 (0)

massive ischemic stroke ($n=1$), and unexpected without obvious etiology ($n=5$).

Acute tolerance

Six patients (6.8%) presented hypersensitivity reaction during cetuximab infusion (four grade 2 anaphylaxis and two grade 4). One of them presented an anaphylactic shock during the fourth infusion complicated with myocardial infarction, and he died one month later during exclusive radiotherapy.

Acute Cet-RT cutaneomucosal toxicity data were available for 67 of 88 patients (14 died before the end of treatment, 5 interrupted cetuximab due to anaphylaxis, data were missing for 2 patients).

Grade 3–4 toxicity was reported in 39 patients (44.3%): mucositis ($n=20$), in-field dermatitis ($n=25$), and out-field folliculitis ($n=10$) (Table 3). Patients with grade 3 or more toxicity had significantly more treatment interruption than those with better tolerance (P value <0.0001).

Thirty-six patients (40.9%) needed unplanned hospitalization during treatment. The main reasons for admission were deteriorated general condition ($n=11$), need of feeding support ($n=9$), mucositis-induced pain management ($n=5$), and dyspnea ($n=4$).

Factor associated with higher rates of toxicity

Tolerance was significantly different depending on the primary site tumor location (P value $=0.041$): Grade 3–5 toxicity was observed in 33.3% of patients with laryngeal primary site, whereas in 87.5% of patients with oral cavity primary site. Patients with hepatic dysfunction had also low-grade 3–5 toxicities (P value $=0.037$).

Analysis of patient characteristics (including age, comorbidities, performance status, nutritional status, smoking or drinking habits, and social isolation) did not suggest any other association with higher toxicity rate.

Clinical response

Three-month clinical response was complete for 28 patients (31.8%) and partial for $n=13$ (14.7%).

Twenty-two patients (25%) presented progressive disease. Others died ($n=14$ during treatment, $n=6$ during 3-month follow-up). There was no significant association between grade 3–5 toxicity during treatment and 3-month objective clinical response (P value $=0.65$). When chemotherapy was contraindicated because of poor general condition, 3-month objective clinical response was significantly lower (P value $=0.039$).

Median follow-up duration was 9.9 months. Median PFS was 6.5 months (95%CI 6.0–10.1), and median OS was 12.8 months (95%CI 8.7–20.2). There was no significant difference in PFS or OS between patients with or without grade 3–5 toxicity: median PFS was 6.4 and 7.8

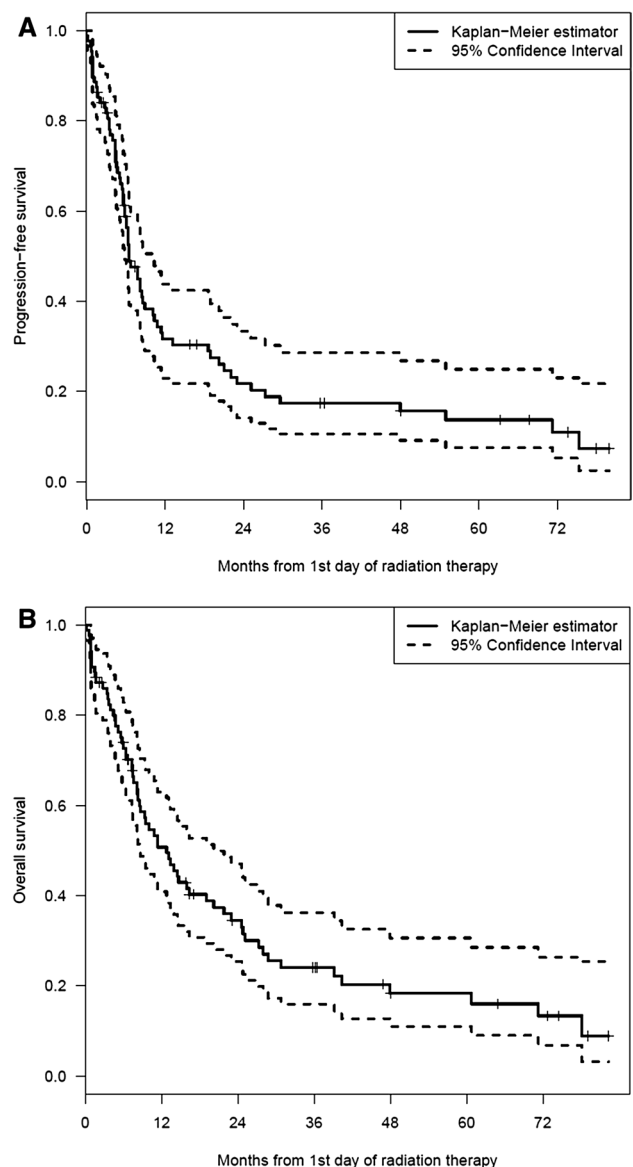


Fig. 2 Progression-free (a) and overall (b) survival

months (P value = 0.48), and median OS was 11.4 and 16.4 months, respectively (P value = 0.32) (Figs. 1, 2).

Discussion

Our goal was to study Cet-RT tolerance in patients ineligible for chemoradiotherapy. Only half of the patients underwent treatment without delay and tolerance analysis revealed 6.8% of hypersensitivity and 44.3% of grade 3–4 mucosal or skin toxicity.

It is noteworthy that retrospective studies are often associated with evaluation bias and missing data. More than a half of our patients presented an oropharynx primitive tumor, in which p16 and HPV status were known to be significant prognosis factors [10–12]. Those statuses might also impact treatment tolerance, but are unfortunately often unknown, because they were not routinely assessed at that time. Nevertheless, this study is to our knowledge the largest one precisely describing Cet-RT tolerance in patient population unfit for CT-RT.

Inclusion criteria for randomized trials always require good general conditions and no organ failure. In our study, contraindication to chemotherapy was related to one up to three comorbidities and 34.04% of patients' performance status was over 2 versus only 10% in Bonner's trial. Moreover, our patients were older than those in Bonner's study (median age: 61 versus 56). The impact of patients' general condition on toxicity has already been reported in prospective [13] and retrospective studies [14, 15]. In cetuximab-treated patients, comorbidities such as undernourishment [16] might increase toxicity risk in the same way as in CT-RT schedules. Despite our high rate of

undernourishment (63.6%), no specific factor has come out in our study, probably because of small subgroups.

Patients description illustrates their frailty. It must be kept in mind that their risk of organ failure remains high whatever the chosen treatment. In the current study, 14 patients died during treatment, most of the time for unknown reason. Cetuximab involvement hardly explains this high rate, knowing that no death had been reported in other studies but one [17]. Furthermore, overall survival reported in our study is 12.8 months versus 49 months reported in Bonner's study, despite the similar disease stages (27.5% of stage III in our study versus 26%), and proportion of tumor localization. This short- and long-term high rate mortality deeply reflects our patients' frailty.

Rate of grade 3–4 cutaneomucosal reaction dramatically differs from one study to another, according to the type of grading and the scale used. It is relevant to notice that Bonner used in 18% of cases a bi-fractionated schedule that lowers in-field acute toxicities. Considering prospective studies and retrospective series with more than 20 patients, dermatitis incidence can vary from 18 to 62.9%, mucositis from 42 to 73%, and folliculitis from 6.5 to 17% [17–22] (Table 4). Our rates of cutaneous side effects are consistent with these data, but our mucositis proportion is notably lower. This is unexpected considering the fact that oral cavity primary tumors were included. It might be due to a misclassification by underestimation of oral toxicity or to different grading scale used.

Considering hypersensitivity reaction, 6 events (6.3%) occurred, 2 of which were grade 4. Only 4 adverse reactions (1.9%) have been reported in Bonner's study, but Magrini [5] and Lefebvre [23] detailed three events (9 and 5%, respectively). Cetuximab hypersensitivity reactions are known to be more frequent and severe in head and neck

Table 4 Studies detailing grade 3–4 toxicity of radiotherapy plus cetuximab association

Author	Year	Journal	Type of recruitment	Population	<i>N</i>	Mucositis	In-field epidermitis (%)	Out-field folliculitis (%)
Bonner	2006	N Eng J Med	Prospective	Selected	211	56	23	17
Walsh	2011	Radioth Oncol	Retrospective	Selected	48	42	18	
Magrini	2015	J Clinical Oncol	Prospective	Selected	35	59	44	
Okano	2013	Jpn J Clin Oncol	Prospective	Selected	22	73	27	
Lefebvre	2013	J Clinical Oncol	Prospective	Selected	56	45	57	
Giro	2009	Radioth Oncol	Retrospective	Unfit	71		49	
Koutcher	2009	Am J Clin Oncol	Retrospective	Unfit	115		23	
Kurokawa	2015	J of radiat research	Retrospective	Unfit	31	48.4	19.4	6.5
Falk	2016	Eur Arch ORL	Retrospective	Unfit	35	31.4	62.9	
Levy	2014	Strahlenter Onkol	Retrospective	Both	71	51	21	
Our study					88	29.7	39.7	13.5

n number of patients included

carcinoma than in colorectal cancer [24]. Systematic anti-cetuximab antibodies blood research may be an interesting way to prevent serious hypersensitivity reaction with 87.5% sensitivity and 82.1% specificity [25].

On the one hand, despite frail population and grade 3–4 toxicity, 47 patients (49.5%) followed schedule without delay, versus 44% in Bonner's; this shows that the treatment remains manageable in unfit population. On the other, 14 patients died during treatment and 26 patients had a modification of treatment schedule with a significant risk of reducing overall survival [26] [radiotherapy suspension 10 days or more ($n=15$), interrupted radiotherapy ($n=6$), and grade 4 anaphylaxis to cetuximab infusion ($n=2$)].

Considering the significantly shorter life expectancy of this population, reducing hospitalization and toxicity risk to improve quality of life by lessening treatment intensity should be discussed. Examining prospectively treatment efficiency and tolerance in unfit population would help target which patients obtain real benefits from Cet-RT.

Conclusion

Balancing expected benefits and risks of Cet-RT is a real challenge in unfit-for-chemotherapy patients. High rate of radiotherapy suspension and mortality should incline in a careful use. Early supportive care has to be provided. It seems necessary now to avoid unrestricted prescriptions and to analyze which subgroups really benefit from this treatment. Prospective cohorts in unfit population would be an interesting element to guide treatment decision.

Compliance with ethical standards

Conflict of interest The authors have declared that no conflicts of interest exist.

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Ethical standards All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional committee and with the 1964 Helsinki declaration and its later amendments.

References

- Calais G, Alfonsi M, Bardet E, Sire C, Germain T, Bergerot P et al (1999) Randomized trial of radiation therapy versus concomitant chemotherapy and radiation therapy for advanced-stage oropharynx carcinoma. *JNCI J Natl Cancer Inst* 91(24):2081–6
- Pignon J-P, le Maître A, Maillard E, Bourhis J, MACH-NC Collaborative Group (2009) Meta-analysis of chemotherapy in head and neck cancer (MACH-NC): an update on 93 randomised trials and 17,346 patients. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 92(1):4–14
- Bonner JA, Raisch KP, Trummell HQ, Robert F, Meredith RF, Spencer SA et al (2000) Enhanced apoptosis with combination C225/radiation treatment serves as the impetus for clinical investigation in head and neck cancers. *J Clin Oncol* 18(suppl_1):47s–53s
- Bonner JA, Harari PM, Giralt J, Azarnia N, Shin DM, Cohen RB et al (2006) Radiotherapy plus cetuximab for squamous-cell carcinoma of the head and neck. *N Engl J Med* 354(6):567–78
- Magrini SM, Buglione M, Corvò R, Pirtoli L, Paiar F, Ponticelli P et al (2016) Cetuximab and radiotherapy versus cisplatin and radiotherapy for locally advanced head and neck cancer: a randomized phase II Trial. *J Clin Oncol Off J Am Soc Clin Oncol* 34(5):427–35
- Petrelli F, Coinu A, Riboldi V, Borgonovo K, Ghilardi M, Cabiddu M et al (2014) Concomitant platinum-based chemotherapy or cetuximab with radiotherapy for locally advanced head and neck cancer: a systematic review and meta-analysis of published studies. *Oral Oncol* 50(11):1041–8
- Walsh L, Gillham C, Dunne M, Fraser I, Hollywood D, Armstrong J et al (2011) Toxicity of cetuximab versus cisplatin concurrent with radiotherapy in locally advanced head and neck squamous cell cancer (LAHNSCC). *Radiother Oncol J Eur Soc Ther Radiol Oncol* 98(1):38–41
- Riaz N, Sherman E, Koutcher L, Shapiro L, Katabi N, Zhang Z et al (2016) Concurrent chemoradiotherapy with cisplatin versus cetuximab for squamous cell carcinoma of the head and neck. *Am J Clin Oncol* 39(1):27–31
- Peddi P, Shi R, Nair B, Ampil F, Mills GM, Jafri SH (2015) Cisplatin, cetuximab, and radiation in locally advanced head and neck squamous cell cancer: a retrospective review. *Clin Med Insights Oncol* 9:1–7
- Ang KK, Harris J, Wheeler R, Weber R, Rosenthal DI, Nguyen-Tân PF et al (2010) Human papillomavirus and survival of patients with oropharyngeal cancer. *N Engl J Med* 363(1):24–35
- Vermorken JB, Psyrri A, Mesía R, Peyrade F, Beier F, de Blas B et al (2014) Impact of tumor HPV status on outcome in patients with recurrent and/or metastatic squamous cell carcinoma of the head and neck receiving chemotherapy with or without cetuximab: retrospective analysis of the phase III EXTREME trial. *Ann Oncol Off J Eur Soc Med Oncol ESMO* 25(4):801–7
- Ou D, Levy A, Blanchard P, Nguyen F, Garberis I, Casiraghi O et al (2016) Concurrent chemoradiotherapy with cisplatin or cetuximab for locally advanced head and neck squamous cell carcinomas: does human papilloma virus play a role? *Oral Oncol* 59:50–7
- Pryor DI, Porceddu SV, Burmeister BH, Guminski A, Thomson DB, Shepherdson K et al (2009) Enhanced toxicity with concurrent cetuximab and radiotherapy in head and neck cancer. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 90(2):172–6
- Koutcher L, Sherman E, Fury M, Wolden S, Zhang Z, Mo Q et al (2011) Concurrent cisplatin and radiation versus cetuximab and radiation for locally advanced head-and-neck cancer. *Int J Radiat Oncol Biol Phys* 81(4):915–22
- Kurokawa M, Watanabe Nemoto M, Harada R, Kobayashi H, Horikoshi T, Kanazawa A et al (2015) Initial experience of radiotherapy plus cetuximab for Japanese head and neck cancer patients. *J Radiat Res* 56(5):849–55
- Denis F, Garaud P, Bardet E, Alfonsi M, Sire C, Germain T et al (2004) 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 Off J Am Soc Clin Oncol* 22(1):69–76

17. Levy A, Blanchard P, Bellefqih S, Brahimi N, Guigay J, Janot F et al (2014) Concurrent use of cisplatin or cetuximab with definitive radiotherapy for locally advanced head and neck squamous cell carcinomas. *Strahlenther Onkol* 190(9):823–31
18. Lord HK, Junor E, Ironside J (2008) Cetuximab is effective, but more toxic than reported in the Bonner trial. *Clin Oncol (R Coll Radiol)* 20(1):96
19. Giro C, Berger B, Bölke E, Ciernik IF, Duprez F, Locati L et al (2009) High rate of severe radiation dermatitis during radiation therapy with concurrent cetuximab in head and neck cancer: results of a survey in EORTC institutes. *Radiother Oncol J Eur Soc Ther Radiol Oncol* 90(2):166–71
20. Okano S, Yoshino T, Fujii M, Onozawa Y, Kodaira T, Fujii H et al (2013) Phase II study of cetuximab plus concomitant boost radiotherapy in Japanese patients with locally advanced squamous cell carcinoma of the head and neck. *Jpn J Clin Oncol* 43(5):476–82
21. Koutcher LD, Wolden S, Lee N (2009) Severe radiation dermatitis in patients with locally advanced head and neck cancer treated with concurrent radiation and cetuximab. *Am J Clin Oncol* 32(5):472–6
22. Falk AT, Hébert C, Tran A, Chand M-E, Leysalle A, Thariat J et al (2016) Radiotherapy for elderly patients and cetuximab, a monocentric study. *Eur Arch Otorhinolaryngol* 274(2):1061–5
23. Lefebvre JL, Pointreau Y, Rolland F, Alfonsi M, Baudoux A, Sire C et al (2013) Induction chemotherapy followed by either chemoradiotherapy or bioradiotherapy for larynx preservation: the TREMPILIN randomized phase II study. *J Clin Oncol Off J Am Soc Clin Oncol* 31(7):853–9
24. Grandvuillemin A, Disson-Dautriche A, Miremont-Salamé G, Fourier-Reglat A, Sgro C (2013) Réseau des Centres Régionaux de Pharmacovigilance Français. Cetuximab infusion reactions: French pharmacovigilance database analysis. *J Oncol Pharm Pract Off Publ Int Soc Oncol Pharm Pract* 19(2):130–7
25. Mariotte D, Dupont B, Gervais R, Galais M-P, Laroche D, Tranchant A et al (2011) Anti-cetuximab IgE ELISA for identification of patients at a high risk of cetuximab-induced anaphylaxis. *MAbs* 3(4):396–401
26. Skladowski K, Law MG, Maciejewski B, Steel GG (1994) Planned and unplanned gaps in radiotherapy: the importance of gap position and gap duration. *Radiother Oncol* 30(2):109–20