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Original Research

Clinical outcomes and prognostic factors in recurrent and/or metastatic head and neck cancer patients treated with chemotherapy plus cetuximab as first-line therapy in a real-world setting

Roberta Depenni [a], Maria Cossu Rocca [b], Daris Ferrari [c], Giuseppe Azzarello [d], Cinzia Baldessari [a], Massimiliano Alù [e], Franco Nolé [b], Carla Codecà [c], Giorgia Boscolo [d], Marco Piccininni [f], Stefano Cavalieri [g], Paolo Bossi [g,*]

[a] *Department of Oncology and Haematology, University Hospital of Modena and Reggio Emilia, Modena, Italy*
[b] *Department of Medical Oncology, Urogenital and Head and Neck Tumors Medical Treatment European Institute of Oncology, Milano, Italy*
[c] *Medical Oncology Unit, ASST Santi Paolo e Carlo, Milano, Italy*
[d] *Medical Specialties Department, Oncology and Oncologic Hematology, ULSS 3 Serenissima Mirano VE Italy*
[e] *Medical Oncology Unit, A.R.N.A.S. Ospedali Civico Di Cristina Benfratelli, Palermo, Italy*
[f] *Department of Basic Medical Sciences, Neuroscience and Sense Organs, University of Bari Aldo Moro, Bari, Italy*
[g] *Head and Neck Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Milan, Italy*

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Prognostic factors

Abstract ***Aim:*** The aims of the study are to evaluate the clinical outcomes of first-line treatment with platinum-based chemotherapy and cetuximab in patients with relapsing/metastatic head and neck cancer (RM HNC) and to identify predictors of treatment response.
Methods: This is a retrospective, observational, longitudinal, real-world study involving 6 oncology centres in Italy. All consecutive patients with RM HNC treated between January 2007 and December 2016 with a first-line therapy consisting of a platinum-based chemotherapy regimen plus cetuximab were included. The primary objective of the study was to assess overall survival (OS) and progression-free survival (PFS). Secondary objectives included

* *Corresponding author*: Head and Neck Medical Oncology Unit, Fondazione IRCCS Istituto Nazionale dei Tumori, Via Venezian 1, 20133 Milano, Italy.
E-mail addresses: depenni.roberta@policlinico.mo.it (R. Depenni), maria.cossurocca@ieo.it (M. Cossu Rocca), daris.ferrari@asst-santipaolocarlo.it (D. Ferrari), azzarello.giuseppe@gmail.com (G. Azzarello), massimilianoclara2004@gmail.com (M. Alù), franco.nole@ieo.it (F. Nolé), carla.codeca@asst-santipaolocarlo.it (C. Codecà), giorgia.boscolo@aulss3.veneto.it (G. Boscolo), marco_piccininni@libero.it (M. Piccininni), stefano.cavalieri@istitutotumori.mi.it (S. Cavalieri), paolo.bossi@istitutotumori.mi.it (P. Bossi).

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the identification of predictors of treatment response.
Results: Overall, 297 patients were identified. Median OS was 10.8 months (95% confidence interval [CI] 9.3–12.2), whereas median PFS was 4.8 months (95% CI 4.3–5.5). On multivariable analysis, independent unfavourable prognostic factors for OS were performance status (PS) Eastern Cooperative Oncology Group (ECOG) >0, presence of residual tumour at primary site, platinum resistance and lack of objective response. Unfavourable predictors for PFS included cancer primary site (paranasal sinuses, hypopharynx), PS ECOG >0, presence of residual tumour at primary site, platinum resistance and lack of objective response. Independent unfavourable predictors of objective response were tumour site (oral cavity, larynx-hypopharynx), residual tumour at primary site and prior chemotherapy.
Conclusions: The availability of new treatment modalities and epidemiological changes make the periodic reassessment of prognostic factors of great relevance to guide clinical practice and the design of future randomised clinical trials.

1. Introduction

Head and neck cancer (HNC) is the sixth most common type of cancer; it represents about 6% of all cases and accounts for an estimated 650 000 new cancer cases and 350 000 cancer deaths worldwide every year [1].

Despite multimodal treatment, 50–60% of stage III–IV cancers relapse locally and/or in distant sites. In the past, different combinations of chemotherapeutic drugs were never shown to prolong overall survival (OS) in these patients [2,3]. In 2008, the phase III trial EXTREME showed for the first time that cetuximab, an anti–epidermal growth factor receptor (EGFR) monoclonal antibody, in combination with a chemotherapy regimen including cisplatin or carboplatin and 5-fluorouracil (5-FU), was able to prolong median survival when compared with chemotherapy alone (10.1 vs. 7.4 months) [4]. A prolongation of progression-free survival (PFS) (5.6 vs. 3.3 months) and a higher percentage of objective responses (36% vs. 20%) were also documented.

Several observational studies have consistently confirmed the benefits of the EXTREME regimen in patients with first-line recurrent and/or metastatic (RM) disease, even if with different patient characteristics, treatment schedules and dose modifications [5–7].

For these reasons, this combination has been considered the standard of care for the first-line treatment of RM HNC [8]. More recently, the favourable results of immunotherapy in first-line setting within the Keynote 048 trial are expected to change the approach to these patients [9]; full results of this trial will shed light on the indication for patients with platinum-sensitive RM disease, also in regard to PD-L1 expression.

The generalisability of platinum combination results to larger, less selected populations still poses some problems. Several doubts persist regarding the therapeutic index of 5-FU, the duration of the combination treatment, the need to comply with the 3-weekly schedule, the optimal dose of platinum and the duration of the maintenance treatment.

Furthermore, the prognostic evaluation of patient candidates for the treatment is based on studies including subjects treated with chemotherapy alone [10]. Whether the same prognostic factors play a role in patients treated with the combination therapy is not known. The periodical re-assessment of prognostic factors is important in a field where the disease is changing from an epidemiological and therapeutic perspective. In particular, the emergence of human papillomavirus-positive cancers and the use of combined therapeutic approaches in curative setting underline the need for up-to-date prognosticators of RM HNC.

Aim of this real-world study was to evaluate the clinical outcomes of first-line treatment with platinum-based chemotherapy and cetuximab in patients with RM HNC and to identify predictors of treatment response and prognosis.

2. Materials and methods

2.1. Study objectives

The primary objective of the study was to assess OS and PFS in patients with RM HNC treated with platinum-based chemotherapy and cetuximab. Secondary objectives included the identification of factors able to predict treatment response and prognosis.

2.2. Study design

This is a retrospective, observational, longitudinal, real-world study involving 6 oncology centres in Italy. The study protocol was approved by the ethics committees of participating centres.

All consecutive patients with RM HNC treated between January 2007 and December 2016 with a first-line

therapy consisting of a platinum-based chemotherapy regimen plus cetuximab were included.

Patients meeting the following inclusion criteria were considered:

- Histologically confirmed squamous cell HNC (cancer of oral cavity, pharynx, larynx or paranasal sinuses or squamous carcinoma of unknown origin with metastases in cervical lymph nodes);
- RM cancer with first-line treatment including platinum-based chemotherapy associated with cetuximab;
- Availability of clinical records

Patients receiving other first-line treatments were excluded.

Information for each patient was collected on an ad hoc, anonymised case report form. The following baseline prognostic factors were investigated: sex, age, site of disease, tumour grading, HPV status for oropharyngeal cancer, performance status (PS), weight loss in the previous 3 months, comorbidities (classified according to Adult Comorbidity Evaluation 27) [11], residual tumour at primary site, previous chemotherapy or cetuximab in curative setting, previous radiotherapy, platinum type, chemotherapy schedule, platinum and cetuximab doublet or with a third drug (i.e. 5-FU or paclitaxel), disease-free interval and platinum resistance (previous platinum administered within 6 months).

Information relative to outcomes included the date of disease progression, date of death and best radiological response during the first-line treatment according to Response Evaluation Criteria in Solid Tumours (RECIST).

2.5. Study end-points

The primary end-points were represented by OS and PFS.

OS was defined as the time between the date of start of first-line treatment and the date of death from any cause; patients alive or lost to follow-up were censored at the date of last visit. PFS was defined as the time between the date of start of first-line treatment and the date of detection of disease progression or death, whichever occurred first. Disease progression was evaluated according to RECIST, version 1.1. Time to disease progression was censored at the date of last visit.

2.6. Statistical analysis

Quantitative variables are reported as mean, standard deviation, median and range, whereas qualitative variables are summarised as frequencies and percentages. Differences between patients who survived more than one year and patients who did not were assessed using the Pearson $\chi 2$ for categorical variables and the Mann–Whitney U-test for quantitative ones. For this analysis, patients censored before 12 months were excluded. For each potential predictor variable, Kaplan–Meier survival functions were estimated, and a log-rank test was used to compare survivorship in different levels of the variable. Survivorship in patients with and without HPV infection was compared only among subjects with oropharyngeal cancer. Predictors with a significant influence ($p < 0.05$) on survivorship in univariate analyses were selected to build three Cox proportional hazards regression models. The first one included as covariates only significant variables of patients' baseline characteristics (site of disease [8 sites], tumour at primary site [yes, no], age categories [quartiles: 25–54, 55–62, 63–70, 71–92], sex [male, female], tumour grading [1, 2–3], comorbidities [0, 1, 2, 3], Eastern Cooperative Oncology Group [ECOG] PS [0, >0], previous radiotherapy [RT] [yes, no], previous computerised tomography [yes, no], previous anti-EGFR [yes, no], disease-free interval [quartiles] and platinum resistance [yes, no]). The second model also included significant variables of baseline therapy (platinum type [carboplatin, cisplatin], number of drugs used [2, >2] and schedule [every week, every three weeks]). The third model additionally included clinical response, only if significant (response categories [complete/partial response, stable/progressive disease]). Furthermore, logistic regression models were run to study the association between clinically relevant baseline variables and additional outcomes represented by the probability of positive clinical response and the probability of surviving one year or more. All statistical analyses were performed using R (v 3.4.3) and Rstudio (v 1.0.153).

3. Results

Overall, 297 patients were identified and included in the analysis. Participant characteristics are reported in Table 1. The median follow-up was 9.4 months (range 1.0–86.1). The median number of cycles of the combination therapy administered was 4 (range 1–8). Percentages of administered prescribed doses are reported in Fig. 1.

Median OS was 10.8 months (95% confidence interval [CI] 9.3–12.2), whereas median PFS was 4.8 months (95% CI 4.3–5.5). The 1-year and 3-year OS rates were 44.4% (CI: 39.0–50.6) and 7.8% (CI: 5.0–12.2), respectively.

Factors associated with OS and PFS at univariate analyses are reported in Table 2.

In univariate analyses, lower OS was associated with PS ECOG>0 ($p < 0.0001$), residual tumour at primary site ($p = 0.0006$), carboplatin use ($p = 0.01$), shorter DFI ($p = 0.03$) and platinum resistance ($p < 0.0001$). Shorter PFS was associated with cancer site ($p = 0.0084$), PS ECOG>0 ($p = 0.0016$), residual tumour at primary site ($p < 0.0001$), shorter DFI

Table 1
Characteristics of the study population (N = 297).

Characteristics	% or mean ± standard deviation
Male gender	72.0%
Age (years)	62.4 ± 10.7
Cancer primary site	
Oropharynx	25.3%
Oral cavity	36.4%
Larynx	23.6%
Hypopharynx	5.4%
Paranasal sinuses	4.0%
Skin	2.0%
Other/unknown	3.4%
Weight loss ≥5%	31.6%
Performance status ECOG	
0	31.7%
>0	68.3%
Residual tumour at primary site (yes)	52.2%
Grading	
1 or 2	46.5%
3	53.5%
HPV positive[a]	71.8%
Number of comorbidities	1.0 ± 0.95
Prior radiotherapy (yes)	79.5%
Prior chemotherapy	
No	48.2%
Induction	9.8%
Induction+concomitant	9.4%
Concomitant	28.6%
Adjuvant	2.0%
Other	2.0%
Prior anti-EGFR (yes)	6.4%
Platinum therapy	
Carboplatin	36.6%
Cisplatin	63.4%
Treatment scheme	
Cetuximab+platinum	45.3%
Cetuximab+platinum+other	49.7%
Chemotherapy treatment schedule	
Weekly	11.8%
3-weekly	88.2%
Best response	
Complete/partial response	35.5%
Stable/progressive disease	64.5%
Disease-free interval (months)	
0–3	31.3%
3.1–6	19.5%
6.1–12	24.2%
12–118	24.9%
Platinum resistant (yes)	16.2%

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.
[a] Oropharyngeal cancer only—data available on 39 of 75 patients.

($p = 0.006$) and platinum resistance ($p < 0.0001$). Patients with complete/partial clinical response to treatment carried a more favourable prognosis, both in terms of OS ($p < 0.0001$) and PFS ($p < 0.0001$).

On multivariable analysis, independent unfavourable prognostic factors for OS were PS ECOG >0, presence of residual tumour at primary site, platinum resistance and lack of objective response (Table 3). Independent unfavourable predictors for PFS included cancer primary site (paranasal sinuses, hypopharynx), PS ECOG >0, presence of residual tumour at primary site, platinum resistance and lack of objective response (Table 3).

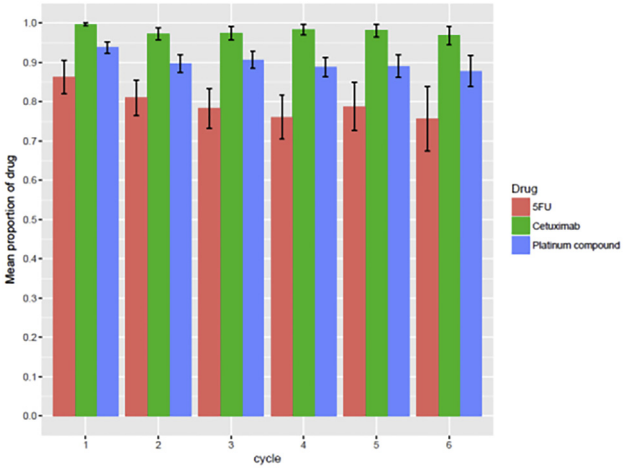

Fig. 1. Percentages of prescribed doses of 5FU, cetuximab and platinum compounds actually administered. 5FU, 5-fluorouracil.

On multivariable logistic regression analysis, independent unfavourable predictors of objective response were tumour site (oral cavity, larynx-hypopharynx), residual tumour at primary site and prior chemotherapy (Table 4).

Finally, patients who survived 12 months or more were compared with those with shorter survival. Table 5 shows patient characteristics according to survival. On multivariable analysis, one-year survivorship was positively associated with an objective response to chemotherapy, whereas the presence of residual tumour at primary site, a PS ECOG >0 and platinum resistance were associated with a significantly lower likelihood of surviving one year or more (Table 6).

4. Discussion

We assessed prognostic factors in patients with RM HNC who received platinum-based chemotherapy regimens plus cetuximab under routine clinical practice conditions. We identified poor PS, presence of residual tumour at primary site and resistance to platinum therapy as independent predictors of poorer OS and one-year survival. These factors retained their prognostic role even after considering objective response, which was in turn associated with a lower risk of death. Poor PS, presence of residual tumour at primary site and platinum resistance were also predictors of poorer PFS, in addition to cancer primary site. The association of these factors with PFS remained significant after adding objective response in the model. The likelihood of an objective response was markedly lower for cancers not located in the oropharynx; furthermore, the presence of residual tumour at primary site and prior chemotherapy halved the likelihood of an objective response.

Table 2
Correlates of overall survival and progression-free survival: univariate analysis.

Factors	Overall survival Median (95% CI)	P	Progression-free survival Median (95% CI)	P
Gender		0.26		0.13
Female	11.1 (8.1–13.3)		4.5 (3.6–6.3)	
Male	10.8 (9.2–12.7)		5.0 (4.4–5.9)	
Age group		0.43		0.74
25–55	12.4 (8.9–16.1)		5.4 (4.5–6.7)	
56–63	11.6 (9.4–15.5)		5.1 (3.6–6.3)	
64–70	9.3 (7.1–12.7)		4.1 (3.2–5.1)	
71–92	9.4 (7.4–11.9)		5.4 (3.9–6.8)	
Cancer primary site		0.20		0.0084
Oropharynx	12.4 (9.5–14.8)		5.5 (4.8–6.9)	
Oral cavity	9.3 (7.5–12.4)		4.1 (3.4–5.8)	
Larynx	11.8 (9.4–15.5)		5.4 (4.7–6.5)	
Hypopharynx	9.3 (4.1–21.8)		4.1 (1.7–7.6)	
Paranasal sinuses	5.4 (3.6-NA)		2.2 (1.4-NA)	
Skin	8.1 (6.0-NA)		3.9 (2.1-NA)	
Other/Unknown	11.2 (7.5-NA)		5.9 (2.7-NA)	
Weight loss		0.19		0.26
<5%	11.1 (9.3–13.3)		5.3 (4.5–6.1)	
≥5%	11.1 (8.0–12.7)		4.5 (3.4–5.9)	
PS ECOG		<0.0001		0.0016
0	16.5 (12.7–21.8)		6.4 (5.4–7.6)	
>0	9.2 (7.7–10.6)		4.3 (3.6–5.1)	
Residual tumour at primary site		0.0006		0.0001
No	12.9 (11.2–14.6)		5.8 (4.9–6.9)	
Yes	8.1 (7.4–10.0)		4.1 (3.2–5.2)	
Grading		0.39		0.091
1,2	11.9 (9.4–13.9)		5.4 (4.3–6.9)	
3	10.8 (8.1–12.7)		4.5 (3.7–5.9)	
HPV[a]		0.39		0.99
Negative	7.9 (7.5-NA)		5.4 (4.2-NA)	
Positive	16.5 (9.3–22.3)		6.0 (3.9–8.9)	
Comorbidities		0.22		0.90
0	11.3 (8.9–13.3)		4.5 (3.6–5.9)	
1	10.0 (8.7–13.8)		4.8 (3.7–6.5)	
2	9.3 (6.7–12.6)		5.1 (4.2–6.6)	
3	11.8 (8.0–22.0)		5.5 (3.9–8.4)	
Prior radiotherapy		0.54		0.21
No	11.3 (7.6–15.5)		4.0 (3.2–5.9)	
Yes	10.2 (9.3–12.4)		5.0 (4.5–5.9)	
Prior chemotherapy		0.68		0.33
No	11.5 (10.0–13.4)		5.2 (4.5–6.4)	
Yes	9.3 (7.7–12.2)		4.5 (3.6–5.5)	
Prior anti-EGFR		0.20		0.48
No	10.2 (9.2–12.2)		4.7 (4.1–5.4)	
Yes	18.1 (9.3–28.3)		6.5 (5.9–10.2)	
Platinum-based treatment		0.01		0.07
Carboplatin	8.7 (7.4–11.2)		4.5 (2.9–5.4)	
Cisplatin	12.2 (9.9–13.8)		5.3 (4.4–6.3)	
Treatment scheme		0.55		0.20
Cetuximab+platinum	9.5 (8.5–11.4)		4.6 (3.6–5.8)	
Cetuximab+platinum+other	11.3 (9.2–13.3)		5.2 (4.3–6.0)	
Treatment schedule		0.97		0.90
1-weekly	9.9 (6.1–15.5)		3.2 (2.8–6.9)	
3-weekly	11.1 (9.3–12.7)		5.0 (4.4–5.8)	
Best response		<0.0001		<0.0001
Complete/partial response	14.6 (12.1–18.5)		7.7 (6.7–9.6)	
Stable/progressive disease	8.1 (7.1–10.5)		3.4 (2.9–4.3)	
Disease-free interval (months)		0.032		0.006
0–3	8.5 (7.4–11.3)		4.1 (3.0–5.2)	
3.1–6	11.2 (7.2–16.1)		3.9 (3.0–6.5)	
6.1–12	10.0 (8.4–13.1)		5.6 (4.5–7.1)	
12–118	12.6 (11.1–19.4)		6.2 (4.8–7.8)	
Platinum resistant		<0.0001		<0.0001

Table 2 (*continued*)

Factors	Overall survival Median (95% CI)	P	Progression-free survival Median (95% CI)	P
No	11.6 (10.5–13.3)		5.4 (4.8–6.3)	
Yes	5.3 (4.1–7.5)		2.5 (1.7–3.9)	

CI, confidence interval; PS, performance status; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.
[a] Oropharyngeal cancer only.

Our study showed median OS and PFS very similar to those observed in the EXTREME [4], confirming the generalisability of trial results. Furthermore, we did not find major differences in OS and PFS according to the chemotherapy schedule or drug combination. The high percentages of prescribed doses actually administered document the feasibility of the treatment in clinical practice.

We allowed a reassessment of prognostic factors for RM HNC in the light of the changing epidemiological and therapeutic scenario. A previous study in patients who received platinum-based chemotherapy regimens without targeted agents [10] identified tumour cell differentiation, ECOG PS, weight loss, prior RT and location of the primary tumour as independent predictors of OS. In our study, the independent predictive role of tumour cell differentiation, weight loss, prior RT and location of the primary tumour was not confirmed. Instead, resistance to platinum therapy and the presence of residual tumour at primary site emerged as important prognostic factors for OS. In line with previous findings [10], we found an association between objective response and overall and one-year survival.

As for PFS, tumour cell differentiation, prior RT and primary cancer site (hypopharyngeal or oral cavity tumours) were previously identified as independent predictors [10]. We found a higher risk of disease progression for cancers of the hypopharynx and paranasal sinuses, whereas none of the other factors evidenced in the study by Argiris et al emerged as

Table 3
Results of multivariable Cox regression models.

Predictors	Dependent variable		
	Overall mortality		
	Model 1	Model 2	Model 3
PS ECOG (>0 vs. 0)	1.69*** (1.28–2.23)	1.65*** (1.24–2.20)	1.68*** (1.26–2.24)
Disease-free interval (RC: 0–3 months)			
4–6 months	0.82 (0.58–1.17)	0.83 (0.58–1.18)	0.83 (0.58–1.20)
7–12 months	0.99 (0.70–1.40)	1.04 (0.73–1.48)	1.05 (0.73–1.50)
13–118 months	0.81 (0.56–1.16)	0.80 (0.56–1.16)	0.90 (0.62–1.30)
Residual tumour at primary site (yes vs. no)	1.43*** (1.10–1.85)	1.48*** (1.14–1.92)	1.47*** (1.13–1.92)
Platinum resistant (yes vs. no)	2.00*** (1.39–2.88)	1.94*** (1.34–2.80)	1.77*** (1.21–2.61)
Platinum therapy (Cisplatin vs. Carboplatin)		0.81 (0.62–1.06)	0.80 (0.61–1.05)
Best response (complete/partial vs. stable/progressive)			0.55*** (0.42–0.73)
	Progression-free survival		
	Model 1	Model 2	Model 3
Cancer primary site (RC: Oral cavity)			
Oropharynx	0.99 (0.73–1.36)	0.99 (0.73–1.36)	1.22 (0.89–1.68)
Larynx	1.10 (0.80–1.51)	1.10 (0.80–1.51)	1.03 (0.74–1.42)
Hypopharynx	1.89** (1.08–3.33)	1.89** (1.08–3.33)	1.74* (0.97–3.10)
Paranasal sinuses	3.68*** (1.95–6.94)	3.68*** (1.95–6.94)	4.64*** (2.33–9.24)
Skin	1.20 (0.52–2.78)	1.20 (0.52–2.78)	1.34 (0.58–3.11)
Other/Unknown	1.56 (0.80–3.05)	1.56 (0.80–3.05)	1.64 (0.84–3.21)
PS ECOG (>0 vs. 0)	1.58*** (1.21–2.05)	1.58*** (1.21–2.05)	1.67*** (1.28–2.18)
Disease-free interval (RC: 0–3 months)			
4–6 months	0.91 (0.64–1.30)	0.91 (0.64–1.30)	0.91 (0.63–1.32)
7–12 months	0.74* (0.52–1.05)	0.74* (0.52–1.05)	0.66** (0.46–0.95)
13–118 months	0.79 (0.55–1.14)	0.79 (0.55–1.14)	0.82 (0.57–1.18)
Residual tumour at primary site (yes vs. no)	1.38** (1.05–1.80)	1.38** (1.05–1.80)	1.26* (0.96–1.64)
Platinum resistance (yes vs. no)	1.78*** (1.25–2.55)	1.78*** (1.25–2.55)	1.66*** (1.15–2.41)
Best response (total/partial vs. stable/progressive)			0.40*** (0.31–0.53)

RC, reference category; ECOG, Eastern Cooperative Oncology Group; PS, performance status.
*p < 0.10; **p < 0.05; ***p < 0.01.
Model 1: only patients' baseline characteristics significant at univariate analysis.
Model 2: patients' baseline and first-line therapy characteristics significant at univariate analysis.
Model 3: patients' baseline, first-line therapy characteristics and clinical response significant at univariate analysis.

Table 4
Correlates of objective response: results of logistic regression.

Correlates	Odds Ratio	95% CI		P
Tumour site (RC oropharynx)				
Oral cavity	0.39	0.20	0.76	0.006
Larynx-hypopharynx	0.31	0.15	0.64	0.002
Other sites	0.47	0.17	1.24	0.14
Residual tumour at primary site (yes vs. no)	0.52	0.30	0.88	0.016
PS ECOG (>0 vs. 0)	1.01	0.57	1.79	0.98
Prior radiotherapy (yes vs. no)	1.58	0.76	3.34	0.22
Prior chemotherapy (yes vs. no)	0.40	0.22	0.72	0.003
Prior anti-EGFR (yes vs. no)	1.32	0.45	3.92	0.62
Platinum therapy (cisplatin vs. carboplatin)	1.69	0.96	3.01	0.07

RC, reference category; CI, confidence interval; PS, performance status; ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

significant prognostic factors in the present analysis; in turn, the role of poor PS, residual tumour at primary site, platinum resistance, and objective response was consistently shown.

However, we caution overinterpretation of the strong predictive role of objective response in our study. Objective response is known to be problematic as a predictor and its coefficient may be inflated, at least partially, by immortal time bias, attributable to misclassified person-time [17]. For this reason, we explored its predictive ability in combination with the other factors in a separate model.

The use of platinum concurrent to RT has been increasing since 2000; it is reasonable that platinum resistance would take the place of previous radiation as prognostic factor in the RM setting. As for weight loss,

Table 5
Patient characteristics according to survival (<12 months vs. ≥12 months).

Characteristics	<12 months	≥12 months	P
Male gender	71.3%	71.3%	1
Age (years)	63.9 ± 10.5	60.5 ± 10.7	0.008
Cancer primary site			0.34
Oropharynx	21.9%	31.2%	
Oral cavity	40.0%	32.0%	
Larynx	21.3%	25.4%	
Hypopharynx	5.6%	4.9%	
Paranasal sinuses	5.6%	2.5%	
Skin	2.5%	0.8%	
Other/Unknown	3.1%	3.3%	
Weight loss ≥5%	32.7%	30.8%	0.84
Performance status ECOG			0.0001
0	21.9%	44.3%	
>0	78.1%	55.7%	
Residual tumour at primary site (yes)	60.6%	40.2%	0.001
Grading			0.42
1 or 2	43.3%	49.5%	
3	56.7%	50.5%	
Number of comorbidities			0.35
0	34.4%	41.0%	
1	36.3%	36.9%	
2	20.0%	12.3%	
≥3	9.4%	9.8%	
Prior radiotherapy (yes)	79.4%	81.2%	0.83
Prior chemotherapy (yes)	55.6%	51.6%	0.59
Prior anti-EGFR (yes)	5.6%	7.4%	0.73
Platinum therapy			0.009
Carboplatin	44.0%	28.1%	
Cisplatin	56.0%	71.9%	
Treatment scheme			0.53
Cetuximab+platinum	47.5%	43.0%	
Cetuximab+platinum+other	52.5%	57.0%	
Treatment schedule			0.94
1-weekly	12.5%	11.5%	
3-weekly	87.5%	88.5%	
Best response			<0.0001
Complete/partial response	25.8%	45.9%	
Stable/progressive disease	74.2%	54.1%	
Disease-free interval (months)			0.17
0–3	35.6%	24.6%	
3.1–6	18.8%	20.5%	
6.1–12	25.0%	25.4%	
12–118	20.6%	29.5%	
Platinum resistant (yes)	23.1%	8.2%	0.0015

ECOG, Eastern Cooperative Oncology Group; EGFR, epidermal growth factor receptor.

Table 6
Correlates of ≥12-month survivorship: results of logistic regression.

Correlates	OR	95% CI		P
Residual tumour at primary site (yes vs. no)	0.50	0.29	0.84	0.01
PS ECOG (>0 vs. 0)	0.41	0.23	0.72	0.002
Platinum therapy (cisplatin vs. carboplatin)	1.63	0.93	2.87	0.09
Best response (complete/partial response vs. stable/progressive disease)	2.06	1.19	3.58	0.01
Platinum resistance (yes vs. no)	0.38	0.16	0.81	0.017

CI, confidence interval; PS, performance status; ECOG, Eastern Cooperative Oncology Group.

it is conceivable that in our study it could have been incorporated in the performance status or that a more intensive approach in terms of nutrition supplements and feeding tube placement could have limited its negative impact. Well or moderate tumour differentiation was previously shown to be an independent negative determinant of outcome in chemotherapy-treated patients [10]. The role of this factor was not confirmed in our study; indeed, the adjunct of cetuximab to chemotherapy could be responsible for this, as in the subgroup analysis of the EXTREME trial the highest benefit of targeted agent was observed in tumours with well or moderate differentiation.

We analysed consecutive, unselected patients treated with platinum-based chemotherapy and cetuximab and tailored treatment combination and schedule. When compared with the EXTREME trial, our patients were older (62 vs. 56 years) and with a higher number of individuals ≥65 years old (41% vs. 18%). While cisplatin was chosen in a similar rate of patients (63% vs. 67%), we included also 2-drug combinations (platinum and cetuximab), treatments with taxane instead of 5-FU as the third drug or schedules considering weekly administration of chemotherapy. Therefore, this analysis closely reflects real life, without an a priori selection of the patients as in randomised phase III trials, whose results may lack external validity [12,13]. The drawback of such a kind of study is clearly the fact that this is not a direct comparison with the EXTREME regimen, in terms of patient population, homogeneity of the adopted treatment and lack of common supportive care strategies during treatment.

The dose intensity of the drugs was quite different, with cetuximab being the highest and 5-FU the lowest. This fact possibly denotes physician attitudes both to start and to lower during the course of the treatment the dose of the drugs perceived as more impacting on toxicity or less influencing outcome. A 3-drug treatment strategy with taxane instead of 5-FU or with a cisplatin and cetuximab 2-drug combination has shown promising activity in a recent large phase II trial [14].

This study provided evidence of the most important prognostic factors influencing OS and PFS in patients treated according to current standards. Although forthcoming immunotherapies could further modify the prognostic profile of patients with RM HNC, the EXTREME scheme still represents the actual standard and could remain one option for patients with contraindications to immunotherapy. Moreover, this study represents the benchmark in real-world setting to be compared with new drug combinations.

We identified platinum resistance as an important unfavourable prognostic factor for OS and PFS, suggesting that early relapse or disease progression after the initial platinum-based therapy could identify a group of patient candidate for immunotherapy. Different from other studies [15,16], we were unable to find HPV as a prognostic factor also in the RM setting. In fact, even if the median OS was 16.5 vs 7.9 months in patients with HPV positive and negative cancers, this difference was not statistically significant. This could be due to the small sample size, as only for 39 of 75 patients the HPV status was available.

Our study has strengths and limitations. Among the strengths, we included a large number of patients treated according current guidelines in real-world setting and followed for a long period of time, thus providing important information on the most relevant prognostic and predictive factors under routine clinical practice conditions. Moreover, the patient population analysed (timeframe 2007–2016) reflects more closely the characteristics of the actual HNC relapsing patients. Among the limitations, it should be considered the retrospective nature of the study, absence of blood biomarkers and the lack of toxicity data, whose analysis would have been limited by the lack of homogeneous way of collection. Furthermore, given the intrinsic explorative nature of our study, overfitting in the models due to the data-driven selection of the variables was likely to occur. Therefore, we acknowledge that the prognostic role of the factors we identified should be confirmed in other independent cohorts of patients.

5. Conclusions

In conclusion, among patients with RM HNC, treated with chemotherapy plus cetuximab as first-line therapy, poor PS, presence of residual tumour at primary site, resistance to platinum therapy and poor response to systemic therapy have a marked impact on prognosis. The availability of new treatment modalities and epidemiological changes make the periodic reassessment of prognostic factors of great relevance to guide clinical practice and the design of future randomised clinical trials.

Conflict of interest statement

Paolo Bossi is a part of advisory boards of/consultant for Roche, Merck, Kyowa Kirin, Astrazeneca, MSD, Angelini and Sanofi. Other authors have nothing to declare.

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