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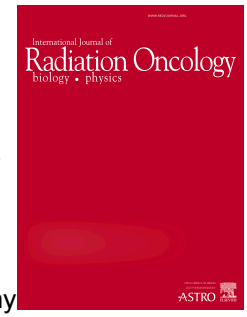

Prospective study of cetuximab, carboplatin and radiotherapy for patients with locally advanced head and neck squamous cell cancer (HNSCC) unfit for cisplatin

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PII: S0360-3016(17)30471-6

DOI: 10.1016/j.ijrobp.2017.02.088

Reference: ROB 24121

To appear in: *International Journal of Radiation Oncology • Biology • Physics*

Received Date: 17 November 2016

Revised Date: 31 January 2017

Accepted Date: 17 February 2017

Please cite this article as: Corry J, Bressel M, Fua T, Herschtal A, Solomon B, Porceddu SV, Wratten C, Rischin D, Prospective study of cetuximab, carboplatin and radiotherapy for patients with locally advanced head and neck squamous cell cancer (HNSCC) unfit for cisplatin, *International Journal of Radiation Oncology • Biology • Physics* (2017), doi: 10.1016/j.ijrobp.2017.02.088.

TITLE PAGE

Title:

Prospective study of cetuximab, carboplatin and radiotherapy for patients with locally advanced head and neck squamous cell cancer (HNSCC) unfit for cisplatin.

Short Title:

TROG cetuximab study

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Conflict of Interest:

COI form completed denoting the support by Merck Serono for this study, namely supply of the drug cetuximab and a study grant of $AUD360,000.00

Acknowledgements:

The author would like to acknowledge and thank the patients who participated in this study, the TROG central office staff, the radiotherapists (Alisha Moore, Michael Ruemelin, and Amy De Smit) and the ROs who contributed to the RT QA (Albert Tiong, Chen Liu, Ieta D'Costa, and Mark Lee), and Richard Young for the laboratory studies. We also thank Merck KGaA, Darmstadt, Germany for their financial

support of this trial. Merck KGaA, Darmstadt, Germany reviewed the manuscript for medical accuracy only before journal submission. The authors are fully responsible for the content of this manuscript, and the views and opinions described in the publication reflect solely those of the authors.

Summary

This is a prospective Phase I/II study reporting on the outcomes of a novel treatment regimen for patients with locally advanced head and neck squamous cell carcinoma (LAHNSCC), fit for curative treatment but not fit for cisplatin. The treatment regimen was delivered in 92% patients, 4 year DFS and OS was 72% and 77%, respectively, there were minimal severe late treatment toxicities. This regimen is feasible and warrants further evaluation.

ABSTRACT

Title:

Prospective study of cetuximab, carboplatin and radiotherapy for patients with locally advanced head and neck squamous cell cancer (LAHNSCC) unfit for cisplatin

Purpose:

To report on the outcomes of a novel treatment regimen for patients with LAHNSCC, fit for curative treatment but not fit for cisplatin.

Material and Methods:

Single arm phase I/II study of previously untreated patients with biopsy proved SCC of the oropharynx, larynx or hypopharynx. The primary endpoint was feasibility of the regimen – defined as the proportion of patients successfully completing treatment. Secondary endpoints were loco-regional control (LRC), failure free survival (FFS), overall survival (OS), and treatment toxicities.

Results:

Sixty patients. Mean age 66 years (range 42-87 years), 28% of patients were >70 years. The median follow-up was 4 years. Compliance with treatment was very high: feasibility was 55/60 (91.7%, 90% CI [83.3% - 96.7%]) which satisfied the pre-defined criteria. The 4 year LRC was 82% (95% CI [71 – 94]), FFS was 72% (95% CI [60 – 85]) and the OS was 77% (95% CI [66-90]). The cumulative incidences of first failure of any type at 4 years were5.2% local, 1.8% local and distant, 8.5% regional, 1.7% regional and distant, 3.5% distant, and 7.7% death (any cause). The 4 year FFS in the 70 years or less and more than 70 years patients were 71% (95% CI [58-

88]) and 73% (95% CI [54-100]), respectively (logrank p=0.801). Their 4-year OS was 79% (95% CI [66-93]) and 73% (95% CI [53-100]), respectively (logrank p=0.708). Significant late treatment toxicities were very few.

Conclusion:

This treatment regimen was feasible and safe in this patient cohort unfit for cisplatin, 28% of whom were older than 70 years. Carboplatin and cetuximab based chemoradiation regimens warrant further investigation in patients with a contraindication to cisplatin.

Introduction

Concurrent chemoradiotherapy (CRT) is a widespread standard of care for non-surgical treatment of locally advanced head and neck squamous cell cancer (LAHNC). Many individual trials and subsequent meta-analyses have shown that concurrent chemotherapy conferred a loco-regional and overall survival benefit compared to patients treated with radiotherapy (RT) alone. [1-4] The majority of the chemoradiation trials have used cisplatin based regimens. The acute toxicity of these regimens is high, and a significant proportion of patients are medically unfit for cisplatin (e.g., deafness, borderline cardiac and/or renal function, peripheral neuropathy).

The optimal chemoradiation regimen for patients medically unfit for cisplatin is unclear. One commonly used regimen of proven benefit was reported by GORTEC (Groupe d'Oncologie Radiotherapie Tete et Cou). In this study patients were randomised to RT alone (70 Gy in 35 fractions) or RT and carboplatin (daily bolus 70mg/m^2 per day for 4 days), and 5-flurouracil (given as a continuous infusion at a dose of 600mg/m^2 per days for 4 days). The chemotherapy cycle was started on days 1, 22, and 43. This phase III study showed improved loco-regional control and overall survival for the chemoradiation arm.[3]

The other common non-cisplatin option in these patients is cetuximab, a monoclonal antibody against the epidermal growth factor receptor. The seminal Bonner study of the combination of cetuximab with RT showed a significant benefit in loco-regional control and overall survival compared to RT alone. [5]

There has been a mixture of other non-cisplatin based regimens reported. There is Australian experience with the "chemoboost regimen"[6]. This regimen included patients medically unfit for cisplatin chemotherapy, utilising carboplatin together with infusional 5-flurouracil (FU) in the final 2 weeks of a 7-week course of RT (70 Gy in 35 fractions). We have also previously reported that in a study of postoperative chemoradiation for resected head and neck cancer, 20/47 (43%) patients were unfit for weekly cisplatin and received weekly carboplatin as an alternative concurrent treatment option. [7] There has been one randomized study in which RT alone was compared to daily single agent cisplatin or carboplatin, and reported improved local control and overall survival in the chemoradiation arms, although the daily administration of chemotherapy is burdensome[8].

The aim of this Phase I/II study was to test the safety and feasibility of a combination treatment regimen suitable for patients with LAHNC who were not fit for cisplatin. A

common standard of care for such patients is the Bonner regimen, to which we added weekly carboplatin , hoping to maintain treatment tolerability and potentially enhance treatment efficacy. Weekly carboplatin was chosen as it is generally well tolerated in this morefrail population, has been previously utilised in HNC [7,8] and does not require the use of central venous catheter devices compared with regimens which contain infusional 5-FU.

The radiotherapy was delivered via the infield boost regimen (IFB), which is similar to the concomitant boost RT schedule which showed a major benefit in an unplanned subset analysis in the Bonner study.

Here we report on the outcomes of this prospective treatment regimen that was conducted under the auspices of the Trans-Tasman Radiation Oncology Group (TROG).

Materials and Methods

This was a single arm phase I/II trial of previously untreated patients with locally advanced (Stage III or IV), biopsy proven SCC of the oropharynx, larynx, or hypopharynx, who were fit for curable treatment but unfit for cisplatin chemotherapy. The primary endpoint was the feasibility of the regimen in this patient cohort. The regimen was considered feasible if it could be safely administered to the study population. Hence feasibility was measured by the “completion rate”, which was defined as the rate of successfully completing treatment. Completion is defined by each of the following 5 criteria being satisfied: 1) at least 94% of the protocol defined dose of radiation being administered; 2) at least 4 out of the 6 planned doses of

cetuximab with RT being administered (in the Bonner study 90% received all planned doses of cetuximab but we did not have any data in combination with carboplatin and RT, so the choice of 4/6 (67%) was an estimate bearing in mind that experience in Australia had reported more toxicity with the addition of cetuximab [11] than reported in the Bonner study); 3) at least 3 of the 5 planned doses of carboplatin with RT being administered (prior clinical experience showed 94% patients received at least 66% of the planned doses [8]); 4) no incident of life-threatening (i.e. grade 4) toxicity; and 5) completion of treatment within one week of the protocol defined duration of radiation, i.e. within 42 days. The secondary objectives were loco-regional control (LRC), failure free survival (FFS), overall survival (OS), and treatment toxicities.

Patients were assessed as medically unfit for cisplatin chemotherapy due to one or more of the following reasons: *clinically* significant sensori-neural hearing impairment (audiometric abnormalities without corresponding clinical deafness were not regarded as a contraindication to cisplatin), severe tinnitus, renal impairment (GFR < 60ml/min), > Grade 2 peripheral neuropathy, inability to tolerate intravenous hydration e.g. due to cardiac disease, co-morbidities (based on clinical judgement by the investigator) associated with ECOG PS 2 that in the view of the investigator would preclude the safe administration of cisplatin. They had to have no evidence of distant metastatic disease (confirmed by a chest/abdominal computerized tomography (CT) or fluorodeoxyglucose (FDG)-Positron Emission Tomography (PET)-CT.. Patients had to be at least 18 years of age and have given signed consent.

Statistical analysis

Calculation of sample size

A completion rate of 80% was deemed to be the minimum satisfactory rate. A rate of 65% would be considered definitely unsatisfactory. The primary endpoint – the completion rate – was assessed by its estimate and an exact 90% 2-sided confidence interval for the observed rate. The regimen would be considered unsuitable if the 90% CI was entirely below 80%, and satisfactory for continued study if the 90% CI was entirely above 65%.The sample size was determined such that if the true rate is 65%, the 90% CI will be below 80% with at least 80% probability and if the true rate is 80%, the 90% CI will be above 65% with at least 80% probability. Performing a power analysis using exact methods, it was determined that the required sample size to satisfy these conditions was 59 patients. To allow for patients who are not fully evaluable, the study aimed to accrue 60 patients.

The Kaplan-Meier product limit method was used to estimate LRC, FFS and OS. All time to event outcomes were measured from the date of registration to the date of the event. Death was a censoring event for LRC.

Site of first failure was assessed as cumulative incidence of first failure, considering each failure separately. Failures were classified as: a) local failure; b) regional failure; c) distant failure and; d) death. Cumulative incidence of first failure of any type was estimated using competing risk model.

Worst grade of toxicity was assessed for each patient and described in tabular form.

As this was a new combination treatment regimen, a Phase I safety component was deployed for the first 6 patients. If one or less patient of the first 6 patients had a dose limiting toxicity accrual could proceed.

Two subsequent subgroup analyses were introduced, one for p16 positive oropharyngeal cancer patients and one for elderly patients (those over 70 years).

All statistical analyses were performed in R (version 3.1.1).

Treatment

Patients were treated with weekly intravenous cetuximab (initial dose of 400mg/m^2 in the week prior to commencing radiotherapy, then weekly 250mg/m^2) and carboplatin (AUC 2) weekly for the duration of the radiotherapy.

The radiotherapy schedule was the IFB regimen - 66 Gy in 35 fractions over 5 weeks. Phase 1 delivered 50 Gy in 2 Gy daily fractions over 5 weeks, encompassing both the gross disease and prophylactic nodal coverage. Phase 2 consisted of a second daily fraction of 1.6 Gy, with a minimum 6 hours inter fraction interval, given to the gross disease with minimum 5mm margin in the last 10 treatment days. All patients were immobilised in a thermoplastic mask and had a planning CT for dose calculation. Non conformal, conformal and later intensity modulated radiotherapy (IMRT) techniques were allowed.

Management of the neck

The protocol dictated that patients who achieved a complete clinical and radiological response in the neck at the 3 month assessment would not have a neck dissection.

Follow-up schedule

Follow-up visits were at 2, 4, 8, 12 weeks post treatment, then every 3 months for the first 2 years, 4 monthly for the third year then 6 monthly until a minimum of 4 years post treatment. A post treatment CT H&N with intravenous contrast and/ or a

PET-CT scan was performed at 12 weeks post treatment, then patients had aH&N CT scan with intravenous contrast every 6 months and annual thyroid function tests.

Quality Assurance

All cases had quality assurance review of systemic therapy and all radiotherapy contours and dosimetry were reviewed by an independent radiation oncologist.

Results

A total of 60 patients were registered between 30/04/2008 and 19/11/2012. Table 1 shows the distribution of baseline characteristics across the 60 patients. The vast majority of patients (86%) were assessed as unfit for cisplatin due to some form of hearing impairment. The median age was 66 years, (42-87 years), with 17 patients (28%) more than 70 years of age. Median follow-up was 4 years and all except 4 patients had at least 2 years of follow-up (minimum protocol follow-up)

As expected, the majority of patients had oropharyngeal cancer (63%), and of those 83% were p16 positive. The majority of patients had a staging PET-CT scan, (56/60, 93%) in addition to a H&N CT scan with intravenous contrast.

Compliance with treatment was very high, as shown in Table 2. Overall 58 patients (97%) received 5 or more of the planned 6 doses of cetuximab. The 2 patients who received less both only had the loading dose of cetuximab, and no carboplatin or radiotherapy. One had a Grade 4 hypersensitivity reaction and refused further treatment; the other revealed an undiagnosed post-traumatic stress disorder and refused further treatment. Three or more cycles of carboplatin was delivered in 57/60 (95%) patients. All 58 patients who continued treatment received 100% of the prescribed RT dose. The radiotherapy technique was conformal in all patients (most

commonly the “horseshoe” technique of fixed 6 fields for 50Gy, then opposing off spinal cord oblique fields for the remaining 20Gy), but IMRT only in 29 (50%).

There were only 3 patients (3/58, 5%) with major RT violations: 2 patients (3%) with D95 of the PTV66 < 95% (<62.7Gy), and 1 patient whose maximum point dose to the mandible was > +7% (>70.6Gy). There were no major protocol violations with respect to RT duration nor the inter fraction interval of at least 6hrs. There were no major systemic therapy protocol violations.

As seen in Table 3, the number of patients satisfying all conditions for feasibility was 55/60 (91.7%, 90% CI [83.3% - 96.7%]) which satisfied the pre-defined feasibility criteria.

The key treatment toxicities are denoted in Table 4. There were no treatment related deaths. The grade 3 mucositis and temporary feeding tube requirements were high as expected, 90% and 78%, respectively; but none of the patients free of disease required ongoing feeding tube nutritional support after 12 months. There were no brachial plexus nor spinal cord toxicity.

The 4 year LRC was 82% (95% CI [71 – 94]), FFS was 72% (95% CI [60 – 85]) and the OS was 77% (95% CI [66-90]). The cumulative incidences of first failure of any type at 4 years were 5.2% local, 1.8% local and distant, 8.5% regional, 1.7% regional and distant, 3.5% distant, and 7.7% death (any cause).

The 4 year FFS for the p16 positive and p16 negative OPC patients were 80% (95% CI [65 – 98]) and 50% (95% CI [22-100]), respectively (logrank p=0.117). The 4 year OS the p16 positive and negative groups were 93% (95% CI [84 -100]) and 50% (95% CI [22-100]), respectively (logrank p=0.031).

The disease characteristics of the 2 age cohorts are shown in Table 5. Compliance with treatment was high in both groups - 93% in patients 70 years or less and 88% in patients more than 70 years. The 4 year FFS in the 70 years or less and more than 70 years patients were 71% (95% CI [58-88]) and 73% (95% CI [54-100]), respectively (logrank p=0.801). See Figure 1.Their 4-year OS was 79% (95% CI [66-93]) and 73% (95% CI [53-100]), respectively (logrank p=0.708).

Discussion

This regimen proved to be safe and feasible in the population of LAHNSCC patients not fit for cisplatin. Treatment toxicities were significant, as one expects with radical HN treatment, but manageable with no treatment related deaths.

Although only 50% patients were treated entirely with intensity modulated radiotherapy (IMRT), the late toxicities were minimal. In particular, there were no patients alive with no evidence of disease who required ongoing feeding tube nutritional support, no brachial plexus injuries, no spinal cord injuries and only 2 cases (3%) of osteoradionecrosis – which included one patient with exposed mandible that healed with observation.

Clarifying what is the optimal CRT treatment regimen in patients who are not fit for cisplatin is of clinical importance, particularly as the aging population continues to grow. In the current study, the mean patient age was 66 years, and 28% of patients were more than 70 years. We didn't find a difference in FFS or OS in the more elderly cohort. Compliance with treatment was high in all patients, including those more than 70 years.

We know from the RTOG 0522 study (8) that concurrent cetuximab adds no additional benefit to concurrent cisplatin. The role of concurrent cetuximab in comparison to concurrent cisplatin is currently uncertain. A recently published prospective randomised study by Magrini et al, comparing weekly cetuximab with weekly cisplatin in LAHNC raised concerns about the efficacy and toxicity of concurrent cetuximab in comparison to concurrent cisplatin. This study closed accrual early (70 patients of a planned 130) and so was underpowered to show a statistically significant difference in outcomes[10]. It has not been until the emergence of human papilloma virus (HPV) related oropharyngeal cancer era that studies have been activated directly comparing concurrent cetuximab versus concurrent cisplatin, and the results of these studies are eagerly awaited (RTOG 1016 NCT01302834;TROG 12.01 NCT01855451;DeESCALaTE NCT01874171). Nevertheless, they will not be directly relevant to optimisation of treatment regimens for patients unfit for cisplatin.

Fortunately, the high acute toxicities and mortality (19%) rates in the cetuximab arm of the Magrini et al study are not the usual experience in the clinical use of cetuximab, and certainly weren't our experience in this current study. Even allowing for the fact that the Bonner study [5] may have underestimated the acute toxicities of concurrent cetuximab, particularly the claim of no increased acute skin toxicities [11] , other studies [9, 12] have not shown anything near the severe hypersensitivity reactions, prolonged treatment interruptions and cetuximab treatment related deaths reported in the Magrini study.

Our original plan, if this regimen was found to be tolerable, was to compare it in a randomised study to the GORTEC regimen for patients unfit for cisplatin. Since that

time there has been reported experience with other regimens that would also be suitable for patients not fit for cisplatin.

One of these is concurrent weekly paclitaxel and carboplatin in the treatment of LAHNC. The doses have varied slightly (weekly paclitaxel dose ranging from 30mg, 40 or 45mg/m^2; and the weekly carboplatin dose from AUC1, AUC1.5 or 100mg/m^2). This chemotherapy doublet has been combined with the concomitant boost radiotherapy regimen [13, 14] and with IMRT [15]. The 3 year LRC rates were very good (72%, 83%, 95%, respectively) and the acute toxicities were high but manageable. It's worth noting that the patients in these studies were younger (mean age 58 years) than our study mean age of 66 years.

GORTEC have presented in preliminary form the results of 2007-01 in which 406 patients (fit for chemotherapy but not necessarily unfit for cisplatin), were randomized to 70Gy over 7 weeks with concurrent cetuximab or concurrent carboplatin, 5FU (as per Calais 1999, [3]) and cetuximab as definitive treatment in LAHNSCC. They showed significantly better loco-regional control and progression free survival in the carboplatin, 5FU and cetuximab arm compared to cetuximab alone, but the difference in overall survival was not statistically significant. These results raise doubts about the adequacy of cetuximab and RT, but it remains unclear whether carboplatin,5FU and cetuximab with RT is superior to the same regimen without the cetuximab. Furthermore, these 2 regimens have not been specifically tested in patients unfit for cisplatin. Moving forward, in patients unfit for cisplatin, it would be clinically useful to compare in a randomised manner our concurrent regimen with that of concurrent carboplatin, 5FU +/- cetuximab, and the concurrent carboplatin/paclitaxel doublet.

Conclusion

This treatment regimen was feasible and safe in this patient cohort unfit for cisplatin, 28% of whom were greater than 70 years. Carboplatin and cetuximab based chemoradiation regimens warrant further evaluation in patients with a contraindication(s) to cisplatin.

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Table 1: Patient characteristics

Variable	**n (%)**
Reason medically unfit for cisplatin	
co-morbidities associated with ECOG PS 2	3 (5%)
inability to tolerate intravenous hydration	3 (5%)
renal impairment	3 (5%)
sensori-neural hearing impairment	34 (57%)
sensori-neural hearing impairment + renal impairment	1 (2%)
sensori-neural hearing impairment + severe tinnitus	6 (10%)
severe tinnitus	10 (17%)
Primary site	
Hypopharynx	6 (10%)
Larynx	16 (27%)
Oropharynx	38 (63%)
p16 status (oropharynx patients only)	
Negative	6 (17%)
Positive	29 (83%)
No tumour	3
Age at Registration (grouped)	
≤ 70 years	43 (72%)
> 70 years	17 (28%)
Gender	
Female	3 (5%)
Male	57 (95%)
ECOG	
0	37 (62%)

1	21 (35%)
2	2 (3%)
T stage	
1	3 (5%)
2	24 (40%)
3	26 (43%)
4a	7 (12%)
N stage	
0	12 (20%)
1	7 (12%)
2a	5 (8%)
2b	21 (35%)
2c	12 (20%)
3	3 (5%)
Stage	
III	14 (23%)
IV	46 (77%)

Table 2: Systemic therapy received

Variable	**statistic**	**n (%)**
Planned first carboplatin dose	Mean (SD)	227 (53)
	Median [range]	225 [133 - 368]
	Interquartile range	180 – 266
Cetuximab doses given (≥80% of prescribed dose)	1	2 (3%)
	5	10 (17%)

	6	48 (80%)
Carboplatin doses given (≥80% of prescribed dose)	0	2 (3%)
	1	1 (2%)
	3	1 (2%)
	4	10 (17%)
	5	46 (77%)

Table 3: Satisfaction rate for each of the conditions necessary for feasibility of the primary objective, considered collectively.

≥ 94% RT dose	**≥ 4 cetuximab doses**	**≥ 3 carboplatin doses**	**No grade 4 toxicity**	**RT duration ≤ 42 days**	**Overall Feasibility**	**n**
FALSE	FALSE	FALSE	TRUE	FALSE	FALSE	2
TRUE	TRUE	TRUE	FALSE	TRUE	FALSE	2
TRUE	TRUE	FALSE	TRUE	TRUE	FALSE	1
TRUE	TRUE	TRUE	TRUE	TRUE	TRUE	55

Table 4: *CTCAE v 3 Treatment toxicities. Number of patients experiencing the toxicity out of 58 patients.

Adverse event	**Grade 2**	**Grade 3**	**Grade 4**
Anaphylaxis			1 (2%)[¥]
Haemorrhage (GI)[£]			1 (2%)
Non neutropenic sepsis		6 (10%)	1 (2%)
Mucositis	5 (9%)	52 (90%)	
Feeding tube (NGT/PEG)		45 (78%)	
Radiation dermatitis	28 (48%)	20 (35%)	
Acne skin reaction	36 (62%)	9 (16%)	
Dry mouth	42 (72%)	6 (10%)	
Nausea	10 (17%)	4 (7%)	
Vomiting	6 (10%)	2 (3%)	
Infection with unknown ANC (Bronchus)		1 (2%)	
Febrile neutropenia		1 (2%)	
Hearing loss		1 (2%)	
Osteoradionecrosis	2 (3%)		
Hypothyroidism	3 (5%)		
Soft tissue Fibrosis	14 (24%)		
Dysphagia > 12 months	15 (26%)		

[¥] Not part of the 58 patients. This was one of the two patients who ceased treatment early.

*CTCAE version 3 (https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/ctcaev3.pdf)

[£] Unrelated to treatment

Table 5: Disease characteristics of the 2 age cohorts.

Variable	**Age ≤ 70**	**Age > 70**
Primary site		
Hypopharynx	2 (5%)	4 (24%)
Larynx	9 (21%)	7 (41%)
Oropharynx	32 (74%)	6 (35%)
T stage		
1	3 (7%)	0 (0%)

2	20 (47%)	4 (24%)
3	17 (40%)	9 (53%)
4a	3 (7%)	4 (24%)
N stage		
0	6 (14%)	6 (35%)
1	5 (12%)	2 (12%)
2a	5 (12%)	0 (0%)
2b	19 (44%)	2 (12%)
2c	6 (14%)	6 (35%)
3	2 (5%)	1 (6%)
Stage		
III	9 (21%)	5 (29%)
IV	34 (79%)	12 (71%)
p16 status (oropharynx patients only)		
Negative	5 (17%)	1 (17%)
Positive	24 (83%)	5 (83%)
No tumour	3	0
Missing	0	0
Treatment feasible		
No	3 (7%)	2 (12%)
Yes	40 (93%)	15 (88%)