Impact Of Early Supportive Care Assessment On Treatment Decision In Head And Neck Cancer Before Concomitant Chemoradiotherapy

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Abstract

Objective: To assess the impact on oncological treatment and supportive care interventions in patients treated with chemoradiation (CRT) for advanced head and neck cancer (HNC) of a global pretherapeutic comprehensive supportive care assessment performed in an outpatient supportive care clinic (OSCC).

Methods: In this monocentric prospective observational study, we included all patients considered for CRT (exclusive or post-operative) for advanced HNC from February 2019 to March 2020. The following frailty indicators were assessed: comorbidities (Charlson Index), nutritional status, altered functional ability (ADL and IADL), social precarity (EPICES score), cognitive impairment (MoCA score), addictive habits and pain.

Results: OSCC led to a change in treatment for 13.7% of patients, mainly de-escalations. Ninety-three percent of patients had at least one altered domain, including 50% with three or more altered domains. Cognitive function was the most frequently altered domain (66.7%). Altered functional ability was significantly associated with treatment de-escalation after OSCC. Treatment interruptions were significantly associated with treatment de-escalation and social precarity. De-escalation was also associated with a significantly poorer PFS (median of 23.2 mos. vs 8.8 mos., HR=2.18 95%IC[1.02- 4.63] p=0.037)) and a non-significant trend towards worse OS (median 23.3mos. vs not reached (HR = 2.16 95%CI[0.88-5.31] p=0.0836).

Conclusion: We strongly encourage the creation of OSCC for patients treated with chemoradiation for HNC. This practice, through an exhaustive assessment, favors therapeutic adaptation, personalized follow-up and optimization of supportive care.

Introduction

Patients with advanced head and neck cancer (HNC) are a population at high risk of frailty. Indeed, smoking and alcohol misuse are the most frequent risk factors and are associated with comorbidities, social precarity and mood disorders [1,2]. Management of locally advanced HNC includes concomitant chemoradiotherapy (CRT) (exclusive or post-operative)[3], which has high rates of acute toxicities leading to 60% of treatment interruptions [4]. However, any deviation from the radiotherapy protocol is associated with poorer outcomes[5,6] : risk of loco regional relapse increases 1-2% per day of interruption and 12-14% per week [7]. Likewise, patients who received only one cycle of cisplatin had significantly lower survival compared to patients who received two or three cycles[8]. We also previously reported in patients treated with radiotherapy plus cetuximab an unscheduled hospitalization rate of 40% [9].

Supportive care is essential in this population to optimize treatments, while maintaining quality of life by limiting toxicities and iterative hospitalizations. Nutritional support is the main intervention as more than 35% of patients are undernourished before any treatment [10,11]. Systematic dietary advice associated with oral supplements have already shown a benefit on CRT toxicities [12]. Early nutritional interventions could limit the rate of malnutrition before and during treatment[11] . From an addictology point of view,

prevalence of alcohol and tobacco use is high in this population (> 75%) [13,14]. Moreover, patients smoking at time of diagnosis and/or during treatment have poorer outcomes [15-16]. Therefore, early substance dependence counseling could improve cessation rates [16,17] and prevent certain complications such as alcohol withdrawal in the event of an unscheduled hospitalization. Finally, social support must also be set up for this often-disadvantaged population [18] as well as for caregivers [19]. HNC patients need diverse and resourceful supportive care.

A dedicated care pathway for head and neck cancer patients treated with CRT has been implemented in the François Baclesse comprehensive cancer center in order to facilitate supportive care access and coordination with community actors[20]. This includes a pretherapeutic comprehensive supportive care assessment in an outpatient supportive care clinic (OSCC) **(supplementary figure 1).** Inspired by comprehensive geriatric assessments[21,22], several points are assessed: nutrition, pain, addiction, functional status, socioeconomic environment, and cognitive screening, and an electrocardiogram and blood test are performed. This assessment is conducted between the first medical oncology consultation and the start of radiotherapy. A medical oncologist, a dietician and an oncology nurse evaluate the patient and refer him to other supportive care specialists if needed (social worker, algologist, psychologist, addiction specialist, etc.). Finally, concomitant treatment is adapted according to clinical findings. The overall assessment is then summarized in the patient file and sent to the general practitioner and community nurse.

The objective of our study is to assess the impact of OSCC evaluation and early supportive care interventions on oncological treatment.

Methods

Study design

This is a single center prospective observational study. All patients received oral and written information regarding the study and gave their consent to the use of their data.

Patients

We included all patients referred by the multidisciplinary HNC team meeting for CRT (exclusive or post-operative treatment) for advanced HNC from February 2019 to March 2020. All patients for whom CRT or RT indication was maintained after OSCC evaluation were included.

Outcomes

We aimed to analyze changes in treatment choice between the first medical oncology consultation and the OSCC evaluation, and the clinical factors associated with these changes. We considered cisplatin the most intensive concomitant treatment, followed by carboplatin-based chemotherapy, and then cetuximab. Patients ineligible for these treatments underwent exclusive radiotherapy. Treatment

modification from one of these treatment groups to the other after OSCC was classified as: no change, escalation or de-escalation.

Our secondary objective was to describe patient frailty and supportive care needs at OSCC evaluation and during CRT. We also assessed CRT completion rates, hospitalization rates, progression-free survival and overall survival.

Frailty indicators were: comorbidities according to the Charlson Index (with a score>5 defined as severe comorbidities)[23,24], nutritional status according to the French National Authority of Health malnutrition (with undernutrition defined as the presence of one or more of the following criteria: >5% weight loss within a month or 10% within 6 months, body mass index <18.5 kg/m2, albumin blood level <35 g/L [25]), functional ability according to Activities of Daily Living (ADL) and Instrumental Activities of Daily Living (IADLs) (a loss of at least one ADL/IADL defined altered functional ability)[26], social precarity was assessed by the EPICES score (with a 30.17 cut-off for vulnerability[27]), cognitive impairment according to Montreal Cognitive Assessment (MoCA) performed by a trained evaluator (with a cut-off value of under 26 for cognitive impairment [28,29]), addictive habits (current misuse of alcohol or smoking), pain (which was considered significant if it required pain therapy modification).

Progression-free survival (PFS) was defined as time from CRT ending to disease progression or last follow-up. Overall survival (OS) was defined as time from CRT ending to last follow-up or death.

Data analysis

Quantitative variables were described by the median value and range [min–max], while qualitative variables were described with numbers and percentages. Chi square or Fisher exact test were used to compare categorical variables. A stepwise logistic regression was used for multivariable analysis. PFS and OS were assessed using the Kaplan–Meier estimator and compared using a log-rank test. A regression of the Cox model was used for multivariate analysis. A two tailed p-value less than or equal to 0.05 was considered statistically significant. MEDCALC software was used for the analysis.

Results

Population

Among one hundred and nine patients evaluated from February 2019 to March 2020, 102 were included **(Figure 1).** Median age was 60 years old [45-72]; 82.4% of patients were male. The predominant tumor sites were oropharyngeal (47.1%) and oral cavity (20.6%) (**Table 1**). Sixty-seven patients (61.5%) had advanced stage IV AJCC (American Joint Committee on Cancer) disease, including 3 patients with stage IVc AJCC oligometastatic disease.

Ninety-five patients (93.1%) had at least one altered frailty domain and 51 (50%) had three or more altered domains (**Figure 2**).

Cognitive function was the most frequently altered domain (66.7%) (**Table 2**). The MoCA test was administered in 87 patients; 12 patients were not evaluated with the test due to tracheo(s)tomy. Test scores were below 26 in 58 patients (66.7%), including 7 patients with a MoCA score below 20.

Addictive habits were frequent. Ninety-seven patients (88.1%) were active or former smokers. Seventy-seven patients (76.2%) declared current or prior alcohol misuse, including 44 with ongoing use (43.6%). Seventy-two patients (71.3%) had a history of tobacco and alcohol co-intoxication, including 25 patients (24.8%) with ongoing consumption of both substances at the time of the study.

Social precarity was reported for 44% of patients according to the EPICES score. Forty-seven (46.0%) patients were single. Twenty-seven patients (26.4%) were unemployed. Sixty-five patients out of 91 (71.4%) did not graduate high school.

Functional ability according to ADL and IADL was altered in 6 and 14 patients, respectively.

Seventy-three (71.5%) patients required analgesic treatment, including 59 patients requiring first step analgesics (according to the WHO analgesic ladder), 29 requiring second step, and 15 requiring third step treatment. Sixteen patients also received neuropathic pain treatment. Eight patients had both level three analgesics and neuropathic pain treatment.

Oncological treatment modalities

Among the 102 included patients, 62 underwent exclusive chemoradiotherapy and 40 received post-operative chemoradiotherapy (**Figure 1**). Concomitant treatment consisted in cisplatin for n=71 (69.6%), carboplatin and 5FU for n=5 (4.9%), and cetuximab for n=13 (12.7%). Ten patients (9.8%) did not receive any concomitant treatment.

A change in the pre-specified treatment was decided after OSCC evaluation for 14 patients (14.4%), with 2 therapeutic escalations and 12 de-escalations.

Patient characteristics (age at diagnosis, gender, tumor site and stage, nutritional status, pain and addiction) did not differ between the two groups (de-escalation versus the rest).

Patients with treatment de-escalation showed a greater number of altered domains than patients with an unchanged or escalated treatment plan (mean of 3.7 versus 2.4, p=0.005). Social precarity, severe comorbidity and altered functional ability were significantly associated with treatment de-escalation (p=0.011, p=0.011 and p=0.027, respectively) (**Table 2**). Only severe comorbidity remained statistically significant in multivariable analysis (OR 7.093, 95%CI[1.107-45.451]).

Supportive care intervention

All patients underwent nutritional assessment by a specialized dietitian during the OSCC, received counselling and follow up during treatment. Before OSCC, 53 (51.9%) patients already benefited from a nutritional intervention with the prescription of nutritional supplements (n=48) and/or enteral feeding (n=13). Additional nutritional intervention was necessary for 55 (53.9%) patients during OSCC: nutritional supplements for 22 patients, enteral nutrition initiation for 33 patients, including immediate nasogastric tube placement for five patients.

Thirty-one patients presented uncontrolled pain requiring treatment adjustment: dose increase or a higher analgesic level for 24 patients, and introduction or a higher dose of neuropathic pain reliever for 14 patients.

Furthermore, 66 patients (64.7%) were enrolled in a closer follow-up program with dedicated nurses during chemoradiation because of frailties detected during OSCC.

Following OSCC, we proposed a consultation with an algologist for n=4 patients (3.9%), a social worker for n=52 (50.9%), a speech therapist for n=7 (6.8%), a tobacco cessation councilor for n=23 (22.5%), an addiction specialist for n=23 (22.5%), and a psychologist for n=29 (28%). We encountered high refusal rates concerning tobacco and addiction specialists and psychologists with only 10 (43%), 5 (21%) and 4 (13%) patients, respectively, accepting these suggested meetings.

Treatment completion and unplanned hospitalizations

Fifty-five (53.9%) patients completed the scheduled treatment: 93/102 (91.2%) patients received their scheduled radiotherapy without interruption, 50/92 (54.3%) patients treated with a concomitant treatment received all the scheduled cycles. Of note, 63 out of 69 patients referred for the cisplatin regimen received ≥200 mg/m² of cisplatin). Six of the nine patients whose radiotherapy treatment was interrupted for toxicities were receiving concomitant cisplatin; the three others were treated with cetuximab.

There was no difference regarding treatment completion between the de-escalation and control groups (33.3% vs 43.3%, p=0.554). Social precarity was significantly associated with CRT interruption in univariate analysis (62.2% versus 34.6% with and without interruption, respectively, among patients with an altered social domain, p=0.010) and multivariate analysis (OR 3.26 95%IC[1.26264-8.427]). No significant association was found regarding other frailty domains or number of altered domains.

Forty-seven patients (46.1%) required a hospitalization during treatment. Main reasons for hospitalization were: nutritional management (n=26), cisplatin-induced nephrotoxicity (n=20), infection (n=10), deterioration of general condition (n=5). No significant association was found with explored frailty domains or number of altered domains. One death, related to septicemia, was reported during the treatment period in a patient of the de-escalation group.

Outcomes

Median follow up was 20.2 months [0.7-28.6]. Fifty-one (50.5%) patients presented disease progression and 29 (28.7%) died. Median PFS was 18.8 months and median OS was not reached.

Median PFS in the control and de-escalation groups were 23.2 and 8.8 months, respectively (HR = 2.18 95%CI[1.02- 4.63] (p=0.037))(**Figure 3**). Regarding frailty indicators, pain and malnutrition were significantly associated with poorer PFS in the univariate analysis (p=0.003 and p=0.021, respectively) (Table 3). Only pain remained significant in the multivariate analysis (p=0.007), but with analyzable data for only 77 patients.

Median OS in the control and de-escalation groups were not reached and 23.3 months, respectively (HR = 2.16 95%CI [0.88-5.31] p=0.084). Regarding frailty indicators, only malnutrition was statically associated with OS in the univariate analysis (p= 0.049), but not in the multivariate analysis (p= 0.391).

Discussion

Our prospective multidisciplinary pretherapeutic HNC assessment involved a change in treatment for 14.4% of patients, mainly de-escalation. Ninety-three percent of patients had at least one altered domain, including 50% with three or more altered domains. Cognitive function was the most frequently altered domain (66.7%). Social precarity, severe comorbidities and altered functional ability were significantly associated with treatment de-escalation during OSCC evaluation in univariate analysis. Only severe comorbidities remained statistically significant in multivariate analysis. Social precarity was significantly associated with treatment interruptions.

After the evaluation of clinician and before OSCC there are still a number of patients (17/102) which remains with an undefined treatment. This highlights the difficulty of assessing a complex patient in a single time-limited consultation. Indeed, this evaluation often requires additional examinations and a multidisciplinary discussion (with a cardiologist for the cardiac evaluation for example). This reinforces the idea of the need for a dedicated time of global reflection of the patient like our study propose.

Our rate of treatment changes after a comprehensive evaluation is lower than in geriatric oncology studies that reported 20-50% change rates[21,22,30]. This was expected as our population was younger and treated in a curative intent whereas these geriatric studies included mostly metastatic patients. Moreover, these geriatric studies reported a large percentage of treatment escalation, whereas 70% of our patients were referred for the highest intensity concomitant treatment before OSCC assessment. Similarly to geriatric oncology studies, treatment de-escalation was associated with comorbidities and altered functional ability [21,22].

Our patients had a high rate of precarity, with the rate of unemployment almost double the general French unemployment rate[31]. Social precarity was significantly associated with CRT interruption, which might be explained by the high intensity of this treatment and the increased reliance on caregivers. Cognitive impairments can impede the adherence to treatment recommendations and lead to toxicity. Furthermore, risk of chemobrain may worsen underlying cognitive impairment [32]. Our high rate of pathological MoCA

score strengthens the need for reinforced follow-up and coordination with community caregivers in this population.

One of the limitations of our study is the lack of depression /anxiety assessment with the use of standardized scores, such as HADS[33]. Indeed, 11-52% of patients present preexisting mood disorders [34]. This is consistent with our 28% referral rate to a psychiatrist or psychologist, without the use of a standardized evaluation tool. Furthermore, mood disorders are frequently associated with coping strategies such as smoking and/or drinking that can increase treatment toxicity and lower its efficacy[15].

We previously reported a high per-treatment mortality rate in unfit patients[9]. This rate has drastically decreased in the present study possibly due to better oncological treatment adaptation and closer follow-up after OSCC evaluation leading to a higher rate of treatment completion. Our PFS and OS are the same as in recent studies with similarly treated patients which is good when we know the hard selection criteria of patients in studies [35,36]. Our de-escalation group had poorer outcomes with a shorter PFS, which was expected given the population's frailty and less intensive treatment.

As this was a unicentric prospective descriptive study, we included patients consecutively to limit selection bias but did not estimate any sample size. Nonetheless, a majority of our patients had stage IV disease, high rates of alcohol / tobacco consumption and few HPV related tumors. Our results may be less relevant in areas where HPV-related carcinoma are predominant and where alcohol / tobacco consumption are less prevalent [37,38].

Our patients presented high rates of cognitive or social frailties and significant comorbidities that justified treatment adaptation. Adding an ADL/IADL index and cognitive screening to the systematic evaluation of our patients can provide valuable information. We strongly encourage the implementation of OSCC prior to CRT for HNC although it requires dedicated medical and paramedical staff and time. It yields high value for therapeutic adaptation, personalized follow-up and optimization of the most suitable supportive care.

Conclusion

For head and neck cancer patients, a multidisciplinary pretherapeutic comprehensive supportive care evaluation before CRT highlighted frailties and led to treatment adaptations for 14% of patients. After OSCC, we were able to implement a more thorough and tailored follow up of patients leading to higher treatment intensity without increasing mortality. Finally, this approach allowed us to be more reactive concerning patients' supportive care needs during their treatment course.

Declarations

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Availability of data and material: Data may be made available upon reasonable request.

Code availability: MEDCALC software was used for the analysis

Contribution Author(s)

Study concepts: Cherifi, Rambeau,

Study design: Cherifi, Rambeau,

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Manuscript preparation: Cherifi, Rambeau

Manuscript editing: Cherifi, Rambeau, Villemin

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All the authors have made a significant contribution to this manuscript, have seen and approved the final manuscript, and have agreed to its submission

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Tables

Table 1 Disease characteristics of the overall population

		N =102	**%**
Primary tumor site	CUP syndrom	10	9,8%
	Oral cavity	21	20,6%
	Oropharynx	48	47,1%
	including p16+	*12*	
	Hypopharynx	9	8,8%
	Larynx	11	10,8%
	Nasopharynx	1	1,0%
	Sinus	2	2,0%
TNM stage (AJCC 8th edition)	**I/II**	17	15,6%
	III	18	16,5%
	IV	67	61,5%

Table 2. Altered domains in the overall population, and comparison of the de-escalation and control groups (univariate and multivariate analysis)

Domain	Global population		De-escalation group		Control group		*p*	*OR[IC95%]*
Cognition	n=58/87	66,7%	n=5/8	62,5%	n=53/79	67,1%	*1*	*0.599 [0,112-3,205]*
Addiction	n=53/102	52,0%	n=7/12	58,3%	n=46/90	51,1%	*0,762*	*2,019 [0,281-14,503]*
Social precarity	n=40/90	44,4%	n=9/12	75,0%	n=31/78	39,7%	***0,011***	*1,274 [0,196-8,236]*
Nutrition	n=33/102	32,4%	n=6/12	50,0%	n=27/90	30,0%	*0,195*	*0,978 [0,162-5,889]*
Pain	n=32/102	31,4%	n=5/12	41,7%	n=27/90	30,0%	*0,509*	*1,962 [0,281-13,711]*
Comorbidity	n=26/102	25,5%	n=7/12	58,3%	n=19/90	21,1%	***0,011***	***7,093 [1,107-45,451]***
Funcitonal ability	n=17/102	16,7%	n=5/12	41,7%	n=12/90	13,3%	***0,027***	*1,240 [0,145-10,602]*

OR[CI95%] : Odds Ratio [95% confidence interval]

Table 3. Median progression-free survival according to alteration of frailty indicators

Frailty indicator	Median PFS if normal	Median PFS if altered	p	HR	CI95%
Comorbidity	23,5	13,9	0,186	1,494	0,768-2,904
Addiction	22,9	17,7	0,434	1,245	0,719-2,155
Functional ability	22,9	13,9	0,58	1,224	0,566-2,647
Cognition	17,1	23,5	0,308	0,727	0,379-1,394
Pain	**26,1**	**10,2**	**0,003**	**2,247**	**1,195-4,227**
Nutrition	**26,2**	**13,1**	**0,021**	**1,897**	**1,033-3,482**
Social precarity	26,1	23,5	0,887	1,046	0,560-1,954

HR : Hazard Ratio; CI95% : 95% confidence interval; PFS: Progression Free Survival

Figures

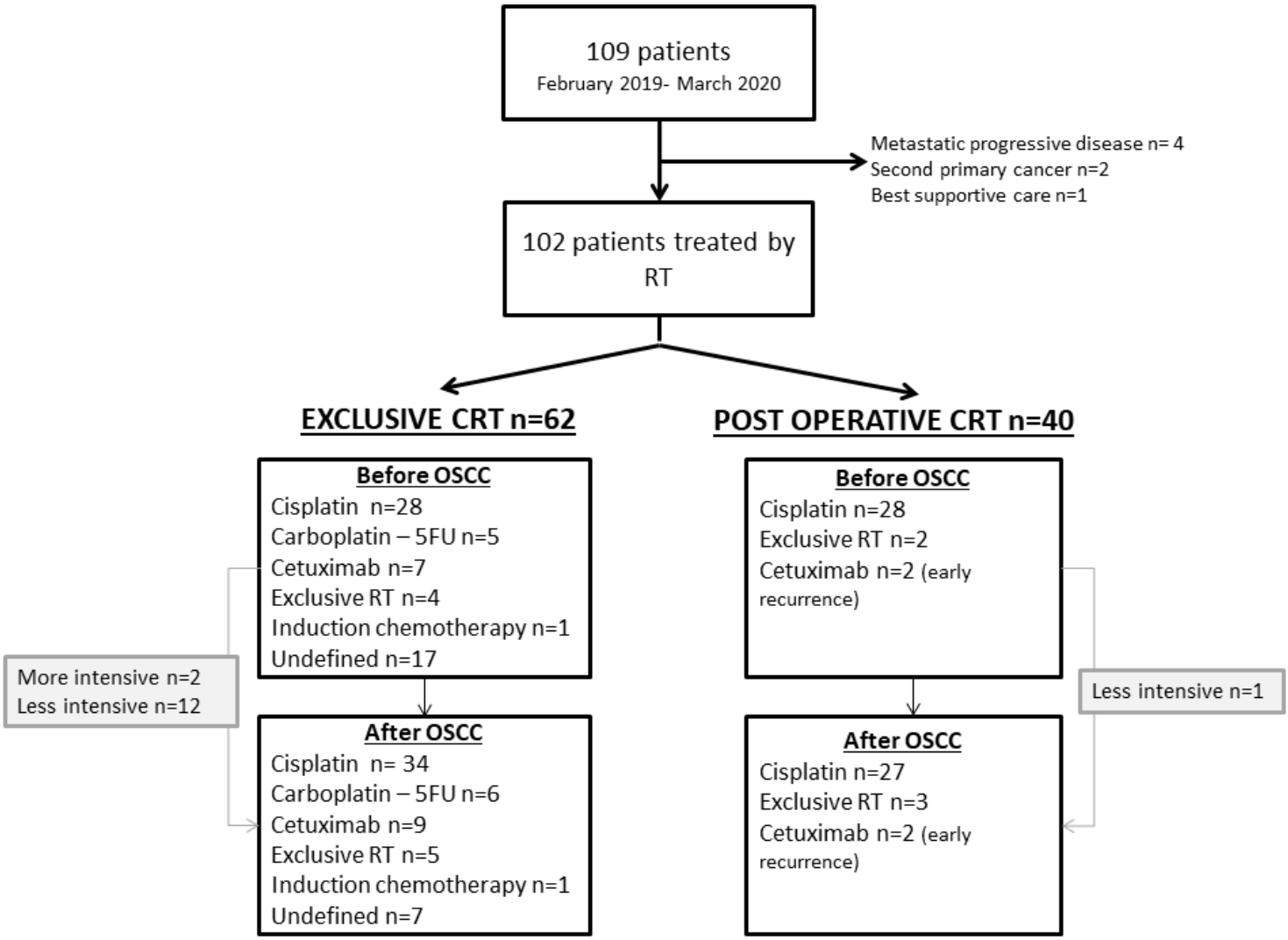

Figure 1

Flow Chart

OSCC : Outpatient Supportive Care Clinic. RT : radiotherapy; CRT : chemoradiotherapy

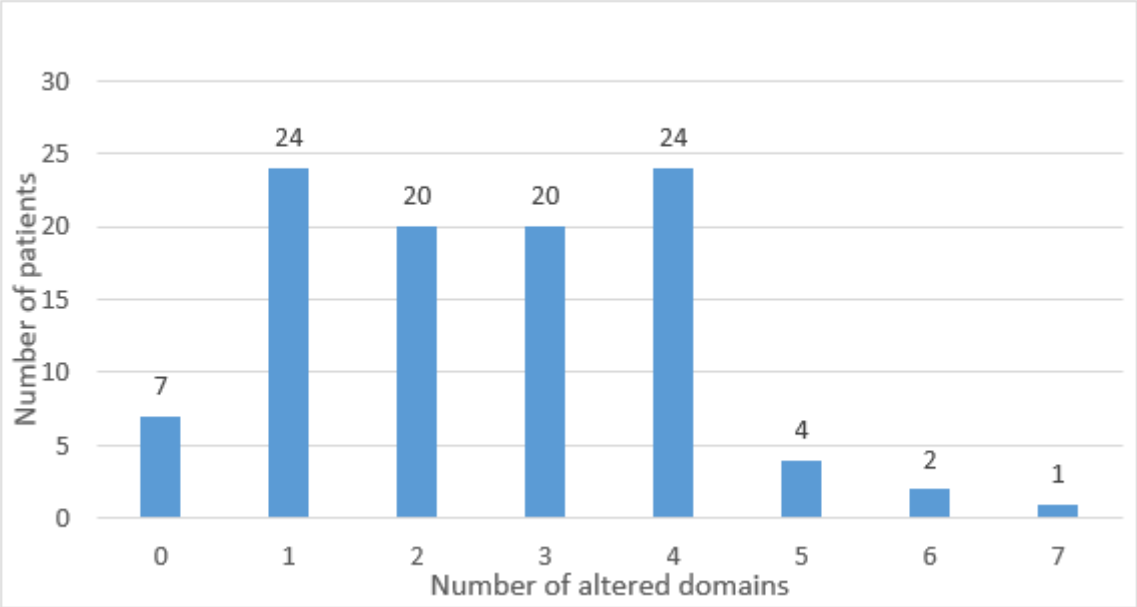

Figure 2

Number of altered domains according to comprehensive evaluation.

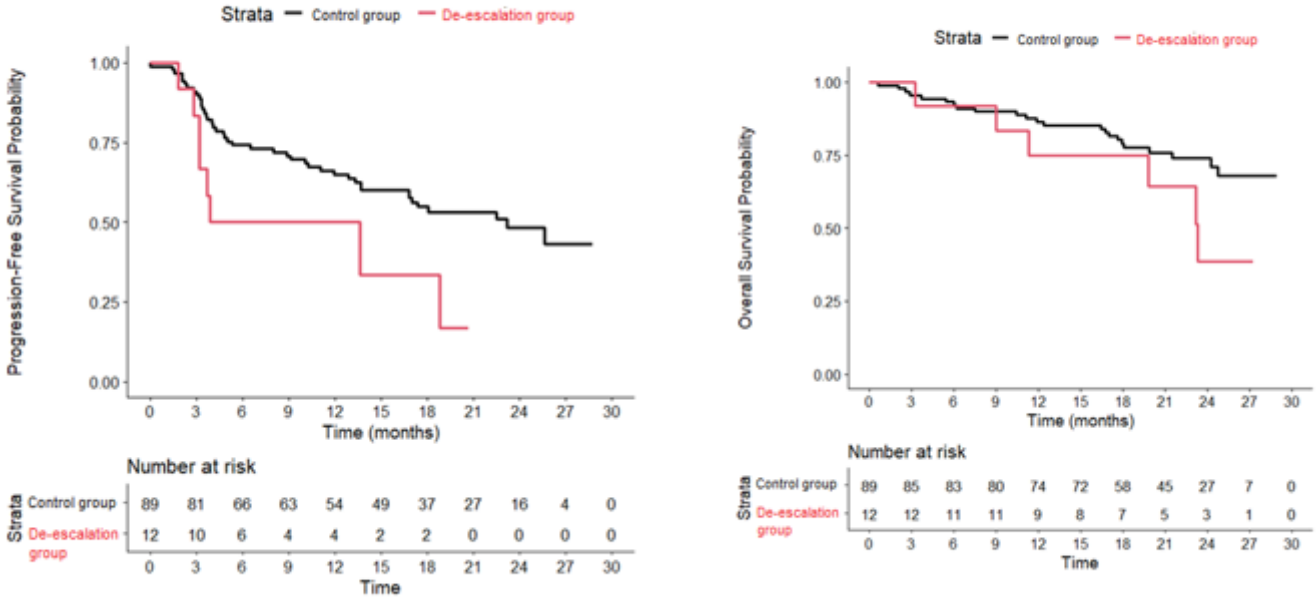

Figure 3

Progression-Free and Overall Survival in De-escalation versus Control group

Supplementary Files

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- Supplementaryfigure1.docx