

HEAD AND NECK

# Head and neck cancer patients declining curative treatment: a case series and literature review

## Rifiuto di trattamenti curativi nel distretto testa-collo: case series e review della letteratura

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### SUMMARY

There is a scarcity of data assessing outcomes of head and neck cancer patients who refuse treatment for potentially curable disease. We report the data of patients who refused curative treatment at a tertiary referral centre and perform a review of the literature. Patients with a potentially curable mucosal head and neck cancers that were discussed at the multidisciplinary tumour board of a referral centre in a two-year period were included. Two cohorts were obtained: patients who accepted the proposed treatment and those who declined it. Statistical analysis was performed using a univariate analysis with parametric and non-parametric tests. Of a total of 803 patients, 14 (1.74%) refused treatment despite being potentially curable. Their median survival was 6.92 months (range 3-12). Patients who refused treatment were older (73.07 years [95% CI, 66.86-79.28] vs 65.56 years [95% CI, 64.70-66.43],  $p = 0.030$ ) and more likely to have T4 disease (50% vs 26.04%,  $p = 0.044$ ). Most patients with curable disease accept conventional treatment and those who refuse it experience dismal outcomes. This report provides objective evidence and can be employed to better counsel patients who refuse curative treatment.

**KEY WORDS:** head and neck cancer, declining treatment, literature review

### RIASSUNTO

**Obiettivo.** I trattamenti per la patologia oncologica del distretto testa-collo possono causare disfunzioni di parola, di alimentazione e alterazione della percezione, esitando spesso in stati ansioso-depressivi che impattano sulla qualità di vita dei pazienti. Talvolta, questi pazienti chiedono che cosa succederebbe nel caso in cui scegliessero di non sottoporsi ad alcun trattamento. Ad oggi c'è una carenza di dati sull'outcome dei pazienti che rifiutano trattamenti per malattie potenzialmente curabili.

**Metodi.** Sono stati inclusi pazienti candidabili a trattamenti curativi con cancro delle vie aereo-digestive superiori discussi nel periodo 2014-2016 presso un centro di terzo livello, e suddivisi in due gruppi: 1) pazienti che hanno accettato il trattamento e 2) pazienti che lo hanno rifiutato.

**Risultati.** Su un totale di 803 pazienti, 14 (1,74%) hanno rifiutato il trattamento. I pazienti del gruppo 2 erano più anziani (73,07 anni vs 65,56 anni,  $p = 0,030$ ), più spesso presentavano una malattia locale T4 (50% vs 26,04%,  $p = 0,044$ ), e la loro mediana di sopravvivenza è risultata essere 6,92 mesi (range 3-12).

**Conclusioni.** Questo studio porta alla luce evidenze oggettive sui pazienti che rifiutano il trattamento per malattie potenzialmente curabili del distretto testa-collo e fornisce elementi utili per dare loro un aiuto efficace ed esaustivo.

**PAROLE CHIAVE:** neoplasie della testa e del collo, rifiuto del trattamento, review della letteratura

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### Conflict of interest

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## Introduction

The morbidity of head and neck cancer treatment can profoundly affect patients and their families. Patients can experience lifelong adverse effects including facial disfigurement and impairment of speech, swallowing, and breathing. These treatment-related sequelae often result in major psychosocial stress leading to high rates of anxiety and depression<sup>1,2</sup>. As a result, it is common that patients hesitate and even initially refuse receiving the proposed therapy after the treatment and its side effects are explained to them. Patients tend to ask about the outcomes of not treating the disease, and what to expect if their cancer remains untreated. There is a scarcity of data assessing outcomes of head and neck cancer patients who refuse treatment for potentially curable disease.

The purpose of this study was to assess the outcomes of head and neck cancer patients who declined conventional curative treatment, to compare their clinical features with patients who accepted the proposed curative-intent therapy and to review the literature on this topic. This information may help both patients and clinicians in decision making by providing information about the expected outcomes of not pursuing standard therapy for head and neck cancer.

## Materials and methods

The London Regional Cancer Program (LRCP) reviews all patients who are diagnosed with head and neck cancers in Southwestern Ontario, encompassing a catchment area of 2 million people. All patients with a suspicion or confirmation of a head and neck cancer are referred to the LRCP and evaluated by a head and neck surgeon and a radiation oncologist in a combined clinic. After the consult, the proposed treatment is communicated to the patient with a detailed explanation of the advantages and side effects of the treatment.

We retrospectively analysed all patients with upper aerodigestive tract malignancies who were referred to LRCP multidisciplinary tumour board from January 2014 till December 2016. Two cohorts were obtained: patients who accepted the proposed treatment and those who declined it. Exclusion criteria included locally advanced unresectable tumours, patients who had metastatic disease and patients harbouring comorbidities that precluded any type of curative-intent treatment (surgical or non-surgical).

The variables analysed included age, gender, marital status, presence of psychiatric illnesses, site, tumour and lymph node staging (according to the American Joint Committee on Cancer [AJCC] 7<sup>th</sup> edition clinical staging criteria), p16 status and overall survival. Comorbidity was measured by the Charlson/Deyo score only in patients who declined

therapy to corroborate that they were amenable to receive treatment. A value of 0 corresponds to no comorbidity; 1 to cardiovascular disease, dementia, chronic pulmonary disease, rheumatologic disease, peptic ulcer disease, mild liver disease, or diabetes; and 2 or greater corresponding to diabetes with chronic complications, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, or AIDS. Causes of death and management of patients who rejected treatment were accounted for.

A T-test was employed for continuous data and chi-squared test for categorical data. Wilcoxon rank sum test was used in cases of non-parametric distribution. Statistical significance was determined at the  $P < 0.05$  level. Data analysis was performed using SPSS 23.0 (IBM Corp., Armonk, NY). Institutional research ethics board approval was obtained for this study (REB# 19-5099.3).

## Results

### *Clinical features of patients declining treatment*

A total of 803 patients were available for analysis. Of these, 14 (1.74%) refused treatment despite being potentially curable. Table I depicts the characteristics of this subgroup. Average age at diagnosis was 73 years (range 55 to 88 years). Nine patients were male. Six (43%) patients were married and two (14%) lived with another family member, whereas the six (43%) remaining patients lived alone with no family support. None had a history of mental illness. The oral cavity was the most common cancer site with 7 (50%) cases, followed by the oropharynx 4 (28.5%), larynx 2 (14.2%) and hypopharynx 1 (7.1%). Most had locally-advanced T-classification, with 7 (50%) T4 cancers. Nearly all [13 (92.8%)] had positive cervical nodes. p16 status was assessed only for oropharyngeal primaries, and three of the four patients were p16 positive. Eleven patients had a Charlson/Deyo score of 1 (five were diabetic and six had cardiovascular disease). The remaining had a score of 0.

### *Survival outcomes*

The median survival for untreated patients was 6.92 months (range 3-12). Comparing cohorts, patients who refused treatment were older (73.07 years [95% CI, 66.86-79.28] versus 65.56 years [95% CI, 64.70-66.43],  $p = 0.03$ ) and more likely to have T4 disease (50% vs 26.04%,  $p = 0.044$ ). There were no significant differences in gender, tumour site, or nodal staging. Table II shows the characteristics of both cohorts. Among the untreated cohort, outcomes for the p16-positive oropharyngeal cancer patients were comparable to p16-negative disease in all sites (7.7 vs 6.7 months, respectively,  $p = 0.4$ ).

**Table I.** Characteristics of patients declining curative treatment.

Age	Gender	Site	T	N	P16	OS	Suggested treatment	Cause of death	Management
77	F	Larynx	4	2a		7	Surgery	Distant metastasis	-
71	M	Oral cavity	4	0		5	Surgery	Distant metastasis	Palliative chemotherapy
88	M	Oral cavity	3	2c		5	Surgery	Local progression	Tracheostomy
88	F	Oral cavity	2	1		4	Surgery	Distant metastasis	-
67	M	Oropharynx	4	0	+	5	ChemoRT	Local progression	Tracheostomy/ G tube
64	M	Oral cavity	4	2c		5	Surgery	Local progression/ distant metastasis	Palliative chemoRT
59	M	Oral Cavity	4	0		12	Surgery	Distant metastasis	Palliative chemotherapy
82	F	Larynx	1	1		12	RT	Pneumonia	-
80	M	Hypopharynx	2	1		6	RT	Local progression	Tracheostomy/ G tube
59	F	Oral cavity	4	2c		3	Surgery	Local progression	Palliative RT
79	M	Oral cavity	4	2b		6	Surgery	Local progression	Palliative RT
55	F	Oropharynx	2	2b	+	8	ChemoRT	Distant metastasis	Palliative chemotherapy
76	M	Oropharynx	3	2c	+	7	ChemoRT	Local progression	-
78	M	Oropharynx	2	2b	-	8	ChemoRT	Distant metastasis	-

**Table II.** Comparison of patients who accepted and patients who declined treatment.

	Accepted	Declined	p value
Age (average)	66.56	73	0.03
Gender (M/F)	589/190	9/5	NS
<b>Site</b>			NS
Oral cavity	267	7	
Oropharynx	203	4	
Larynx	163	2	
Hypopharynx	30	1	
Nasopharynx	23	-	
Other	103	-	
<b>T stage</b>			(T4 vs T3-1) 0.044
T1	216	-	
T2	239	4	
T3	136	3	
T4	198	7	
<b>N stage</b>			NS
N0	354	1	
N1	69	4	
N2a	75	3	
N2b	137	2	
N2c	101	4	
N3	53	-	

Causes of death of patients who declined treatment were distant metastasis in seven cases, local progression in six patients and one case of aspiration pneumonia. Management of this cohort included palliative treatment for local symptoms and systemic therapy, all in the context of very advanced diseases after initial treatment refusals. Supportive and comfort measures such as palliative care, tracheostomy and G-tube placement were also implemented (Tab. I). Fifty percent of the patients were managed at the hospital or hospice and the remaining were managed at home by palliative care services.

## Discussion

A unique feature of head and neck malignancies is that both the disease and treatment carry frequent acute and late toxicities that can have profound effects on patients' quality of life. Facial disfigurement, impaired oral intake and speech alterations predisposes patients to social isolation and depression <sup>1</sup>. Therefore, after a diagnosis is made and the treatment and its side effects are presented to the patients and their families, they face the difficult decision of undergoing curative therapy with the possibility of high morbidity, accepting palliative treatment, or declining treatment altogether in hopes of maintaining quality of

life<sup>3</sup>. In the internet era, patients have access to a myriad of information including the promises offered by alternative treatments from unreliable sources.

Our data has shown that 1.7% of patients presenting to our multi-disciplinary clinic elected to decline any conventional treatment, including three patients with highly curable HPV-positive disease. We found that these patients tended to be older and more likely to have T4 disease than patients who accepted the recommended therapy. The use of alternative medicine treatment was not well documented in the clinical notes; however, the senior investigators note that interest in pursuing alternative medicine was a frequently cited reason for treatment refusal. This paper serves to provide objective evidence for future patients that while conventional treatment has significant toxicity, refusal almost uniformly leads to a rapid demise.

There have been few attempts to analyse the subset of patients who refuse treatment. Kowalski et al.<sup>4</sup> published an experience of 797 patients with a wide range of tumour staging including unresectable and metastatic tumours, who refused any sort of treatment in a tertiary referral centre in Brazil. With a median overall survival of 3.82 months (range 1 day to 4 years), they found that the only predictor for increased overall survival was higher performance status. In their cohort, 19% of patients refused treatment based on their personal choice, whereas the remaining had advanced untreatable tumours or poor health status that precluded treatment. Another single institution experience from Great Britain<sup>5</sup> included 44 patients who received no form of treatment. In that study, median survival was 2.8 months (no range was provided) and they found no significant differences between overall survival and patient demographics, AJCC staging, or interventions such as tracheostomy or gastrostomy tube. In their series, only four (9%) patients were amenable to be cured (one of them being 92 years old) but refused treatment. The remaining patients harboured metastases or comorbidities that made them unsuitable for treatment. There were no “control groups” (comparison with patients who accepted the proposed treatment) in these reports.

More recent studies employing large databases have been published. A multi-institutional analysis by Choi et al.<sup>6</sup> using the Korean Health Insurance Review and Assessment Service, identified 605 head and neck cancer patients between 2003 and 2013. Surprisingly, 32.2% were left untreated. The median overall survival was 9 months, with advanced age at diagnosis the only significant risk factor for decreased overall survival in a multivariate analysis. Comparing patients who refused with those who accepted treatment, they found that advanced age at diagnosis, lower socioeconomic status, and lip and oral cavity loca-

tions were risk factors associated with patient refusal. Stage, comorbidities and tumour histology were not analysed. Hughley et al.<sup>3</sup> employed the Surveillance, Epidemiology, and End Results (SEER) cancer registry program between 1983 and 2011 and identified patients diagnosed with upper aero-digestive tract cancers, including only patients aged 70 and older at the time of diagnosis. A total of 35,834 patients was obtained with 3589 (10%) being untreated patients. The median overall survival was 4 months for the untreated cohort, but risk factors for overall survival were not analysed. Higher stage, primary pharyngeal site and black race were all significant predictors of untreated status. Finally, Cheraghlou et al.<sup>7</sup> included only patients with resectable oral cavity malignancies using the National Cancer Database (NCDB) from 2004 till 2012. Their total cohort was constituted by 36,261 patients, in which 356 (1%) were untreated. The median overall survival in this case was 13.7 months, with advanced age, higher T and N stages, comorbidities, and government insurance being significant risk factors for decreased survival of patients declining treatment in a multivariate analysis. Factors associated with treatment refusal in their final model were: higher T and N stages, age > 75 years, treatment at low/intermediate volume facilities and those with no insurance or government insurance. All patients had resectable tumours, but they did not consider comorbidities which might have precluded treatment. Table III summarises the findings of these studies.

Our study represents, to our knowledge, the first report to include both resectable and operable patients only, all of whom refused treatment despite being potentially curable. Our overall survival was within the range of prior studies (2.8<sup>5</sup>-13.7<sup>7</sup>). Patients declining treatment tended to have more advanced local disease<sup>6,7</sup> (present study), which is understandable as the curative treatment implies more extensive procedures with higher morbidity and disfigurement and may have led to treatment refusal. On the other hand, treatment refusal with higher stages can be related more with the fact that patients already have a negligent and denial component that results in choosing to not receive treatment. Advanced age at diagnosis was also frequently reported as a significant factor<sup>6,7</sup> (present study). We had two 88-year-old patients, which were deemed treatable and curable based on their low comorbidity scores and after being assessed by the multidisciplinary tumour board. At our centre, age per se does not represent an absolute limitation for offering curative treatment, and decisions are made based on patient health status, desires and treatment morbidity. The relation between advanced age and not receiving treatment has to be carefully interpreted as advanced age may be confounded by comorbid conditions that impede treatment.

**Table III.** Review of the literature of previous reports.

Source/Study years	Location	Pt N (% from the total cohort)	Inclusion criteria	Reasons for no treatment	Overall survival (months)	Significant factors for overall survival (in untreated patients)	Risk factors for not receiving treatment
Kowalski et al./1953-1990	Brazil Tertiary Referral Centre	797 (100%)	UADT SCC, no oncologic treatment	Unresectable tumours (603/74.6%) Clinical status (52/6.4%) Patient refusal (153/19%)	3.82 (1d-54)	Performance status	No control group
Jeannon et al./2006-2007	Great Britain Tertiary Referral Centre	44 (9%)	UADT SCC, no oncologic treatment	Unresectable tumours (16/36%) Clinical status (24/54%) Patient refusal (4/9%)	2.8	None	No control group
Choi et al./2002-2013	Korea National Database	195 (32%)	UADT, no oncologic treatment	Not provided	9	Advanced age	Advanced age Lower SE status Oral cavity locations
Hughley et al./1983-2011	United States National Database	3589 (9.7%)	UADT, >70 y.o., no oncologic treatment	Not provided	4	Not analysed	Higher stages Lower SE status Black race Pharyngeal site
Cheraghlou et al./2004-2012	United States National Database	356 (1%)	Oral Cavity SCC, no oncologic treatment, resectable tumours	Patient refusal (356/100%)	13.7	Advanced age Higher stages Increased comorbidities Government insurance	Higher stages Age > 75 Low or intermediate volume facilities No insurance or government insurance
Sahovaler et al./2014-2016	Canadian Tertiary Referral Centre	14 (1.7%)	UADT, no oncologic treatment, resectable tumours	Patient refusal (14/100%)	6.9 (3-12)	Not analysed	Advanced age Higher T stages

UADT: upper aerodigestive tract.

Although we were unable to do a pair-matched analysis to compare our cohorts, ours was the only study that included only potentially curable and fit patients, and this allowed us to compare the dismal median overall survival of our series (6.92 months; range 3-12) with the outcomes reported in the literature in similar populations who underwent a curative treatment. In a recent series of 244 patients affected by oral cavity carcinoma (stage I-IV, mean age 63.8 years), 5-year OS was 60.5%<sup>8</sup>, whereas none of our patients survived more than a year. An experience from our centre showed that even in patients with recurrent oral cavity cancer treated with salvage surgery, 5-year OS was 43%<sup>9</sup>, and even higher than in our cohort. Differences with OS of oropharyngeal malignancies are even more notorious, with a reported 3-year OS between 87%-82% in HPV+ and 57.1%-41% in HPV- patients<sup>10,11</sup>. Even in recurrent cases, 5-year OS was higher

than 50% in a recently published meta-analysis<sup>12</sup>. Patients harbouring laryngeal cancer recurrences treated with salvage laryngectomies have a 2 year OS of 71% after organ preservation therapies have failed. All this surmises that the option of not receiving evidence-based curative treatment carries a much worse prognosis, even in the recurrent setting.

In some jurisdictions, socioeconomic status and its derivatives (e.g. type of insurance) may play an important role in not treating patients<sup>3,6,7</sup>. This is intimately related with advanced stages at diagnosis, and even in countries with universal access to healthcare system<sup>13</sup>, individuals with lower socioeconomic status have more limited access to primary care and periodic health examinations. Oral cavity<sup>6</sup> and pharyngeal<sup>3</sup> locations were treated in smaller proportions in two studies. A potential explanation with the oral cavity location is that treatment gener-

ally include extensive surgical approaches, which result in discouraging patients, even though advanced presentations already cause a certain degree of disfigurement. We cannot justify the pharyngeal location as they are initially treated non-surgically, which can be perceived less morbid for the general population. In previous studies, p16 status of patients was not commented on. In our cohort, there were three patients with HPV related oropharyngeal carcinomas, and surprisingly their overall survival was similar to the rest of the cohort, given that they tend to progress more indolently.

Limitations of this study are represented by the small sample size, retrospective nature of the study and the fact that some patients who refuse any sort of treatment before being referred to the LRCP multidisciplinary tumour board would not be captured in the study. Moreover, we were not able to account for other variables which might have impacted on patients' decision such as financial status and the exact reason for treatment refusal was not specified in patients' charts.

## Conclusions

The vast majority of patients with curable head and neck cancers accept conventional treatment. However, a small minority refuse therapy and experience dismal survival outcomes. These patients are more likely to be older with advanced T stage disease. P16 + patients did as poorly as P16 negative head and neck cancer patients. This study provides objective evidence of the risks of refusing conventional therapy and can be used to counsel future patients who are considering declining treatment.

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