Direct healthcare costs of oral cancer: A retrospective study from a tertiary care center

Davide Bartolomeo Gissi [a,*], Carlota Suàrez-Fernandez [b], Roberto Rossi [a], Francesco Vitali [c,d], Alice Marzi Manfroni [c,d], Andrea Gabusi [a], Luca Morandi [e,f], Tiziana Balbi [g], Lucio Montebugnoli [a], Maria Pia Foschini [h], Achille Tarsitano [c,d]

[a] *Department of Biomedical and Neuromotor Sciences, Section of Oral Sciences, University of Bologna, Bologna, Italy*
[b] *Department of Surgery and Medical-Surgical Specialities, School of Medicine and Health Sciences, University of Oviedo, Oviedo, Spain*
[c] *Oral and Maxillofacial Surgery Unit, IRCCS Azienda Ospedaliero-Universitaria, Bologna, Italy*
[d] *Department of Biomedical and Neuromotor Sciences, Section of Maxillofacial Surgery at Policlinico S. Orsola-Malpighi, University of Bologna, Bologna, Italy*
[e] *Functional and Molecular Neuroimaging Unit, Bellaria Hospital, Department of Biomedical and Neuromotor Sciences, University of Bologna, Italy*
[f] *IRCCS Istituto delle Scienze Neurologiche di Bologna, Bologna, Italy*
[g] *Unit of Anatomic Pathology, S. Orsola Hospital, IRCCS Azienda Ospedaliero-Universitaria, Bologna, Italy*
[h] *Department of Biomedical and Neuromotor Sciences, Section of Anatomic Pathology at Bellaria Hospital, University of Bologna, Bologna, Italy*

ARTICLE INFO

ABSTRACT

The aim of this study was to retrospectively evaluate the direct costs of OSCC treatment and postsurgical surveillance in a tertiary hospital in northeast Italy.

Sixty-three consecutive patients surgically treated for primitive OSCC at S. Orsola Hospital in Bologna (Italy) between January 2018 and January 2020 were analyzed. Billing records of the Emilia Romagna healthcare system and institutional costs were used to derive specific costs for the following clinical categories: operating theatre costs, intensive and ordinary hospitalization, radiotherapy, chemotherapy, postsurgical complications, visits, and examinations during the follow-up period. The study population comprised 17 OSCC patients classified at stage I, 14 at stage II, eight at stage III, and 24 at stage IV.

The estimated mean total direct cost for OSCC treatment and postsurgical surveillance was €26 338.48 per patient (stage I: €10 733, stage II: €19 642.9, stage III: €30 361.4, stage IV: €39 957.2). An advanced diagnosis (stages III and IV), complex surgical procedure, and loco-regional recurrences resulted in variables that were significantly associated with a higher cost of OSCC treatment and postsurgical surveillance.

Redirection of funds used for OSCC treatment to screening measures may be an effective strategy to improve overall health outcomes and optimize national health resources.

1. Introduction

Oral cancer is a general term that refers to a group of malignant tumors that can affect the lips, tongue, right and left cheek, upper and lower gingiva, and hard and soft palate. According to Globocan, the estimated number of cases and deaths attributable to oral cancer in Italy in 2020 were 4037 and 1583, respectively (Sung et al., 2021). Despite its relatively low incidence, oral cancer is a major public health concern. Currently, only 30% of oral cancers are detected at early stages (I and II), and in 40% of cases diagnosis is formulated before locoregional metastasis to other sites (SEER,).

The 5-year survival rates have remained unchanged (in Italy, 57% for the period 2005–2009) (AIOM), and surgical management often causes significant disease-related and treatment-related side effects that impair breathing, swallowing, speech, and nutrition. Furthermore, the development of a recurrence or a second primary cancer after surgery (a leading cause of cancer-related death) ranges from 17% to 30%, which is higher than any other type of tumor (Brocklehurst and Speight, 2018).

Studies analyzing the costs of illness in OSCC have recently gained increasing importance. Although the patient's clinical benefit should

remain the primary aim for treatment planning, the evaluation of the disease's economic burden is of primary interest for decision makers involved with healthcare policy, resource allocation, and establishing research priorities.

The economic burden of OSCC can be divided into the following categories:

- Direct medical costs, which include the costs of diagnosis, treatment, and follow-up care. Treatment may involve surgery, chemotherapy, radiation therapy, or a combination of these.
- Indirect and intangible costs, which may include costs related to reduced productivity and income due to illness, disability, or premature death. The emotional and psychological burden of OSCC, the pain and suffering experienced by the patient and their loved ones, and so-called financial toxicity all fall within this category (Hussaini et al., 2022).

Recently, heterogeneous studies have evaluated the direct costs of OSCC care across the world (Pollaers et al., 2019; Zavras et al., 2002; Polesel et al., 2019; Huang et al., 2020; Singh et al., 2021; Ribeiro-Rotta et al., 2022; Milani et al., 2021; Nijdam et al., 2004; van Agthoven et al., 2001; Porta-Vázquez et al., 2023). Most studies have analyzed patients with head and neck cancer, including carcinoma of the oral cavity, oropharynx and/or larynx and salivary glands; however only a few investigations have focused exclusively on patients diagnosed with carcinoma of the oral cavity and lip. Furthermore, the sources of data may differ. Some studies have analyzed the economic burden of head and neck carcinoma, beginning with institutional or administrative databases, while others have been based on reviews of clinical records. Databases produce data from larger cohorts of patients, but are less likely to generate useful and specific clinicopathological variables influencing healthcare costs.

Finally, it is important to highlight that the economic burden of OSCC can also vary by geographic location, since healthcare costs and productivity losses differ according to the country or region. Most studies come from the USA (Lairson et al., 2017; Epstein et al., 2008; Wissinger et al., 2014), while only very few studies have been conducted in Europe (Zavras et al., 2002; Polesel et al., 2019; Ribeiro-Rotta et al., 2022; van Agthoven et al., 2001; Porta-Vázquez et al., 2023). Specifically, only one study has analyzed the costs relating to patients affected by head and neck carcinoma (including the oral cavity) in Italy (Polesel et al., 2019), evaluating the direct healthcare costs, from diagnosis to treatment, of 879 patients affected by head and neck carcinoma through an institutional database.

Within this background, the aim of our study was retrospectively to evaluate the direct costs of oral cancer treatment at a tertiary Italian hospital in Bologna, Italy. Specifically, as well as specific disease survival, the relationship between disease stage, direct costs, and post-surgical complications were evaluated.

2. Materials and methods

2.1. Study population

This retrospective observational study was conducted at Sant'Orsola-Malpighi Polyclinic Hospital in Bologna, Italy. Consecutive patients with clinical and histological diagnosis of oral squamous cell carcinoma (OSCC), who were surgically treated in the Oral and Maxillofacial Surgery Unit between January 2018 and January 2020 were considered for the present study. All participants gave their informed consent.

The inclusion criteria were as follows:

- Histological diagnosis of oral squamous cell carcinoma of the oral cavity, including tongue, lips, floor of the mouth, buccal mucosa, gingival tissues, hard and soft palate, retromolar area, and tuber maxillae.

- First presentation of OSCC within the study period.
- Surgical OSCC resection with curative intent, with or without adjuvant chemotherapy or radiotherapy.
- A total follow-up period of 3 years.

Patients with a history of oral cavity tumors were excluded, as were those with head and neck carcinomas of the nasopharynx, oropharynx, and hypopharynx.

In total, 63 cases were deemed suitable for inclusion in the study population.

2.2. Treatment modality

All patients were assessed by a multidisciplinary team involved with head and neck cancer, composed of maxillofacial surgeons, otolaryngologists, plastic and reconstructive surgeons, radiation and medical oncologists, pathologists, radiologists, and allied healthcare personnel. After the diagnostic workup and multidisciplinary discussion, all 63 patients underwent surgical resection of OSCC in accordance with the standard treatment practice (Kademani et al., 2005). Surgery was tailored according to the clinical stage, and consisted of composite resections, including excision of the primary tumor with ipsilateral or bilateral neck dissection, depending on the N-status.

Both primary closure and local flap placement were performed for early stages. Microvascular reconstruction was performed in patients with locally advanced disease. Postoperative adjuvant therapies were performed according to the currently accepted guidelines for head and neck cancer (Caudell et al., 2022). Postoperative radiotherapy usually consisted of a 30-session cycle, and had to be undertaken within 7 weeks after surgical treatment, following a planning CT or PET-CT scan, depending on the T and N status of each patient. Intensity-modulated radiotherapy (IMRT) was used, with a dose ranging from 50 to 63 Gy, depending on the risk of disease recurrence and anatomical site. Concomitant chemotherapy consisted of three to six cycles of cisplatin for all patients.

Clinical follow-up was performed every 2 months for the first year after treatment, every 3 months during the second year after surgery, and,finally, every 6 months. A CT or MRI scan of the head and neck region was requested every 6 months during the first 3 years after surgery, and then once a year, according to our internal guidelines.

2.3. Data collection

The first step was to compile a de-identified, confidential, and password-secured database of clinicopathological features of each patient, from diagnosis to 3 years post-diagnosis. Clinicopathological information included: age; sex; smoking habits; ASA status; tumor location; diagnosis date; date of surgical treatment (oral cancer excision); TNM stage classification, according to AJCC criteria (8th edition) (Amin et al., 2017); histological grade, defined according to Kademani et al. (2005); need and type of maxillofacial surgical reconstruction; adjuvant radiotherapy and chemotherapy; length of surgical treatment (in minutes); length of intensive and ordinary recovery (in days); and need for adjuvant radiotherapy and/or chemotherapy. All patients' postoperative visits, postoperative CT or MRI examinations, management of treatment complications, investigations for recurrence, and treatments of recurrence were included.

The study population was classified into four disease stages according to the AJCC criteria (8th edition) (Amin et al., 2017).

2.4. Cost analysis and calculation

Billing records for the Emilia Romagna healthcare system were used to derive costs, except for operating theatre costs. For this reason, the hospital charges of the regional healthcare system did not accurately reflect the true healthcare costs. Since hospitals are subsidized by the

state, charges are grossly underpriced to accommodate the Italian healthcare system policy of providing universal hospital coverage. An institutional cost of €30 per minute of theatre time was considered, as previously described (Tarsitano et al., 2016a).

Psychological and social work outpatient visits were not included in this study. Outpatient dental care was provided by external institutions, so costing data were not available for this analysis. Table 1 shows the exact price values relating to clinical categories. For each patient, the costs relating to surgery, hospitalization, adjuvant radiotherapy and chemotherapy, follow-up visits, and appearance of complications were calculated.

2.5. Statistical analysis

Demographic and clinical parameters and scales were summarized using classic descriptive statistics. Non-parametric (chi-squared and Fisher's exact) tests were used to evaluate any between-group differences (stage I vs stage II vs stage III vs stage IV) in demographic, surgical, and postsurgical characteristics of the study population. One-way ANOVA analysis with multiple-range test and chi-squared analysis were used to evaluate any between-group significant differences (stage I vs stage II, stage III, stage IV) in terms of costs. A multiple linear regression with stepwise selection was fitted for the entire study population to evaluate the relationship between costs and the following variables: age ($<65/>65$), gender (male/female), smoke (no/yes), ASA status (ASA 1–2 vs ASA 3–4), tumor location (tongue and floor of mouth/cheek/gingiva and hard palate), grading (G1/G2/G3), T stage (T1–2/T3–4), N stage (N0 vs N+), stage of disease (stage I vs other stages), radiotherapy (yes vs no), chemotherapy (yes vs no), surgical reconstruction (no flaps vs local flaps vs microvascular flaps), surgical complications (yes/no). A Cox proportional hazard model was fitted to

Table 1
Cost calculations relating to clinical category.

Treatment	Characteristics	Mean cost	Reference
Surgery	Operating room cost per minute, including medical staff, nursing staff, and equipment.	€30 per min	Institutional cost
Intensive therapy	Intensive care room cost per day, including equipment, nursing and medical staff, drugs, nutrition, and accommodation costs	€1383 per day	Emilia Romagna regional healthcare system
Hospitalization	Hospital stay cost per day, including equipment, nursing and medical staff, treatment, catering, and accommodation costs	€615 per day	Emilia Romagna regional healthcare system
Chemotherapy	Average cost for 3–6 cycles of cisplatin	€383.5 (3–6 cycles)	Emilia Romagna regional healthcare system
Radiotherapy	Cost of 30 sessions of radiotherapy	€5670 (30 cycles)	Emilia Romagna regional healthcare system
Follow-up visits	Cost of a follow-up visit to the maxillofacial unit, where the standard protocol is: - 1st year, one every 2 months - 2 nd year, one every 3 months - 3rd, 4th, and 5th year, one every 4 months	€18 for visit	Emilia Romagna regional healthcare system
CT scan	Cost of CT scan; the standard protocol for this instrumental exam is: - 1st, 2nd, and 3rd year, one every 6 months - 4th and 5th year, one every year	€142.05 for CT scan	Emilia Romagna regional healthcare system

confirm the association between disease specific survival and stage of disease. Values of $p < 0.05$ were considered to reflect a statistical significance for all analyses.

3. Results

3.1. Study population

Of the 63 patients included in the study population, 33 were males and 30 were females, with a median age of 69.6 ± 11.9 years (range 39–91). Twenty of the 63 patients were smokers and 43 were non-smokers. Tumor locations were as follows: tongue in 21 of 63 (33.3%) patients; floor of mouth in seven (11.1%) patients; cheek in 12 (19%) patients; soft palate in one (2%) patient; upper gingiva in four (6.3%) patients; lower gingiva in 15 (23.9%) patients; and lower lip in three (4.8%) patients.

TNM was evaluated according to the p-TNM classification of tumors (AJCC 8th ddition). Seventeen patients were diagnosed as T1N0, one as T1N1, 14 as T2N0, one as T2N1, six as T3N0, two as T3N1, two as T3N2, two as T4N0, six as T4N1, four as T4N2, and eight as T4N3. Consequently, 17 patients were classified as stage I, 14 as stage II, eight as stage III, and 24 as stage IV. None of the patients included in the study cohort showed distant metastases at presentation, except for one patient who had a lung metastasis 3 months after surgical excision of the tumor mass.

Surgery consisted of surgical resection of the tumor with primary closure for 15/63 (23.8%) patients. Local flaps were performed in 22/63 (34.9%) patients to obtain an adequate oral reconstruction. Finally, microvascular reconstruction was performed in 26/63 (41.3%) patients. The median time for surgical resection and reconstruction was 370.9 min (minimum 10 min, maximum 1000 min).

The median duration of postsurgical hospitalization (including intensive care unit and ordinary hospitalization) was 13.5 (range 0–50) days. A total of 50/63 (79.4%) patients required postsurgical hospitalization in the intensive care unit.

Thirty-four (54%) patients were treated with surgery alone, whereas 29 (46%) were treated with adjuvant radiotherapy. Nine out of 63 (14.3%) patients received concomitant chemoradiotherapy. During follow-up, postsurgical complications appeared in of 18/63 patients. Specifically, 16 of these were registered as locoregional complications and two were reconstruction-related complications. Eighteen of the 63 patients (28.6%) experienced a second locoregional neoplastic manifestation — in particular: six patients had a local relapse; five had a regional relapse; four had both local and regional relapses; and three developed lung metastasis. Twelve of the 17 patients who experienced relapses died of the disease. Two of the 63 died from different diseases. Table 2 describes the features of the study population in relation to disease stage.

3.2. Costs and prices analyses

The estimated mean total direct cost for OSCC treatment and postsurgery surveillance was €26 338.5 (range €1386.3–70 473) per patient. One-way ANOVA detected a significant difference between stages of disease ($F = 22.79$; $p < 0.001$). Post hoc analysis performed to compare the effect size for different stages showed that stage I presented a significantly lower mean patient cost compared with other stages (Fig. 1).

Table 3 describes the differences between clinical disease stages in terms of mean costs and minimum–maximum ranges for patients. One-way ANOVA analysis showed a significant difference between stages of disease with regard to cost of surgical treatment, cost of intensive and ordinary therapy, and cost of adjuvant radiotherapy and chemotherapy.

Multilevel mixed logistic regression analysis revealed that advanced diagnosis (stages III and IV), complex surgical procedure based on microvascular flap, and locoregional recurrences resulted in variables

Table 2

Characteristics of the study population in relation to disease stage; bold entries indicate statistically significant *p*-values.

|		Stage I	Stage II	Stage III	Stage IV	*p*-value
Sex	Males	8	9	5	11	0.63
	Females	9	5	3	13	
Age	<65	5	1	2	10	0.15
	>65	12	13	6	14	
Smoke	Yes	11	10	6	16	0.94
	No	6	4	2	6	
ASA status	ASA I	0	0	0	0	0.21
	ASA II	3	1	3	2	
	ASA III	14	12	5	22	
	ASA IV	2	22	0	24	
Site	Tongue and floor of mouth	10	4	5	9	0.21
	Cheek	2	4	2	4	
	Upper and lower gingiva, and hard palate	3	4	1	11	
	Soft palate	1	0	0	0	
	Lip	1	2	0	0	
Grading	G1	8	5	1	1	0.05
	G2	8	7	6	18	
	G3	1	2	1	5	
Surgical procedure	No flaps	10	5	0	0	**< 0.001**
	Local flaps	7	5	3	7	
	Microvascular flaps	0	4	5	17	
Median length of surgery (min)		125.7 (range10–340)	293.6 (range 18–500)	460 (range 25–820)	560 (range 230–1000)	**< 0.001**
Intensive therapy	Yes	7	12	7	24	**< 0.001**
	No	10	2	1	0	
Median time of intensive and ordinary hospitalization (days)		5.6 (range 0–22)	8.1 (range 0–19)	11.920 (range 2–22)	20 (range 7–48)	**< 0.001**
Radiotherapy	Yes	1	1	6	21	**< 0.001**
	No	16	13	2	3	
Chemotherapy	Yes	1	1	2	4	0.46
	No	16	13	6	20	
Surgical complications	Yes	5	5	1	8	0.68
	No	12	9	7	16	
Relapse	Yes	4	3	2	9	0.47
	No	13	11	6	15	
Median follow-up period (months)		31.2 ± 10.7	31.9 ± 10.7	30.4 ± 10.7	23.5 ± 14.4	0.11
Survival	Died of disease (DOD)	1	2	2	10	**0.03**
	Alive	16	12	6	14	
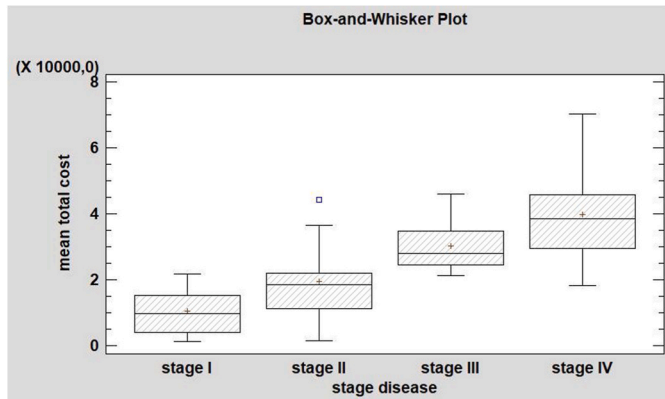
Fig. 1. Box plots obtained using total costs calculated for each stage of disease, showing a significant difference between the groups (one-way ANOVA analysis: $F = 22.79$; $p < 0.001$).

being significantly associated with a higher cost of OSCC treatment and postsurgical surveillance.

4. Discussion

In this retrospective study, the direct costs relating to multimodal treatment and follow-up of patients diagnosed with squamous cell carcinoma of the oral cavity in an Italian cohort of patients from a tertiary Italian hospital were calculated. As mentioned previously, the management of oral cancer poses significant economic challenges due to complex treatment regimens and associated healthcare costs. In our study, an average cost of €26 338.5 per patient — 77% of the annual salary of an Italian person — was calculated for multimodal treatment and management. The analysis of costs stratified by stage revealed significant cost differences between stages, ranging from an average cost of €10 733 for patients diagnosed with stage I to €39 957.1 for patients with advanced diagnosis (stage IV).

Polesel et al. (2019) reported similar data in their unique study, which analyzed the direct costs of head and neck cancer treatment in Italy. The authors calculated an average cost per patient of €20 184, ranging from €12 958 for stage I patients to €26 000 for stage IV patients. Interestingly, both Italian papers demonstrated substantial agreement, despite the presence of significant differences in the study designs: Polesel et al. analyzed a population of patients affected by head and neck cancer (including oral cavity, hypopharynx, and larynx), whereas our study focused exclusively on patients treated for squamous cell carcinoma of the anterior part of the oral cavity. Furthermore, the results of the Polesel et al. study were obtained from a population-based database, whereas in our case information was obtained from the clinical medical records of a single tertiary hospital. Finally, the study populations derived from two Italian regions (Friuli Venezia Giulia and Bologna in Emilia Romagna). In Italy, the universal health service is widely funded by the central government, but the 20 Italian regional authorities are responsible for organizing and delivering health services. This implies the possibility of differences in costs and treatments among the 20 regions of Italy.

Lower direct costs were reported in a European study that analyzed direct healthcare costs for a population study of patients diagnosed with

Table 3

Mean, minimum, and maximum cost (in euros) per patient according to clinical disease stage; bold entries indicate statistically significant *p*-values.

	Stage I	Stage II	Stage III	Stage IV	*p*-value
Cost of surgical treatment	3771.18 (300–10 200)	8809 (540–15 000)	13 800 (750–24 600)	16 801.3 (6900–30 000)	**< 0.001**
Cost of intensive care recovery	650.8 (0–2766)	1185.4 (0–1383)	1383 (0–2766)	1613 (1383–2766)	**< 0.001**
Cost of ordinary recovery	3472 (0–13 530)	4963.9 (0–11 685)	7303 (1230–13 530)	12 505 (4305–29 520)	**< 0.001**
Cost of adjuvant therapy (radiotherapy and chemotherapy)	356.1 (0–5670)	432.4 (0–5670)	4348.4 (0–5670)	5025.2 (0–5670)	**< 0.001**
Cost of instrumental examinations during follow-up period	726.9 (142.05–852.3)	740.7 (0–852.3)	710.3 (142.05–852.3)	526.8 (0–852.3)	0.07
Cost of follow-up visit	206.5 (54–234)	208.3 (18–234)	202.3 (72–234)	158.3 (0–234)	0.31
Complications and secondary tumor treatments	8775 (0–11 505)	11 560 (0–24 370)	6971 (0–19 068)	7259.3 (0–37 518)	0.9
TOTAL	**10 733 (1386–21 894.3)**	**19 642.9 (1626–44 461.5)**	**30 361.4 (21 262–46 136.7)**	**39 957.1 (18 294–70 473)**	**< 0.001**

squamous cell carcinoma limited to the oral cavity, based on clinical records derived from a Greek hospital. The authors estimated an average direct cost of €7450 (including diagnostic tests, such as biopsies and imaging studies, surgery, chemotherapy, radiation therapy, and hospitalization), corresponding to 65% of a Greek person's annual salary (Zavras et al., 2002). Zavras et al. (2002) also reported significant cost variations based on clinical stage, ranging from €4088.9 for stage I to €12 803.7 for stage IV.

Despite similar average direct costs per patient reported in two other studies that analyzed direct costs for patients treated for head and neck cancer in Europe, heterogeneous results have been reported in studies conducted in non-European countries. Specifically, van Agthoven et al. (2001) estimated an average cost of €25 543 in a study conducted in two major hospitals in the Netherlands, whereas in the UK, the estimated cost amounted to approximately €23 500 for the first 2 years of treatment (Kim et al., 2011). In contrast, in studies in India and Iran, the median costs per patient were 170 343 INR (€1904.74) (Singh et al., 2021) and $9022 (€8307.10) (Rezapour et al., 2018), respectively.

Not surprisingly, the direct costs emerge to be higher in countries with higher living costs. Pollaers et al. (2019) reported a mean cost of AU$92 958 (€57 137.66) in Australia, whereas Lairson et al. (2017) estimated $139 749 (€128 548.12) for the management of oropharyngeal cancer patients in the USA.

Our data, in agreement with previous reports, confirmed the economic burden of oral cancer treatment on the healthcare system. Similarly, the rising increase in costs during disease progression emphasizes the importance of early diagnosis and intervention, not only for patients' survival and quality of life but also for decision making relating to healthcare policies, resource allocation, and research priorities.

In our study, only 17 cases were diagnosed with stage I (26.9%), 14 with stage II (22.2%), eight with stage III (12.7%), and 24 with stage IV (38.1%). Importantly, data from this study suggest that a simple transition from stage I to stage II implies a significant increase in costs (average cost for stage I of €10 733 vs average cost for stage II of €19 642.9). This suggests the need for cost reduction policies involving the adoption of strategies to improve early diagnosis in oral cancer management.

In many cases, oral cancer at an early stage is asymptomatic and mimics benign conditions. However, despite the evidence that the cost-effectiveness of oral cancer screening programs remains insufficient to support their institutionalization, potential benefits exist. Indeed, high-risk patients could be recognized and treated during the premalignant phases of the disease (oral potentially malignant disorders, OPMD) or early-stage cancers, thus reducing mortality. Conventional oral examination and incisional biopsy with histological assessment are the current methods for identifying and monitoring high-risk patients. Both methods have limitations relating to the clinical experience of practitioners and the invasive nature of incisional biopsy. To improve early OSCC detection rates, several non-invasive diagnostic aids have been

proposed, including technologies that use dyes, autofluorescence, toluidine blue, and non-invasive sampling procedures based on saliva or brushing cell collection for analysis of molecular markers) (Morikawa et al., 2020; Giovannacci et al., 2016; Brocklehurst et al., 2013; Gissi et al., 2021). Studies evaluating the economic implications of oral cancer screening programs (i.e. with the use of non-invasive diagnostic aids) are necessary to improve the knowledge gap regarding their clinical advantages and cost effectiveness in the management of OSCC patients (Raman et al., 2023).

Additionally, data from our study revealed a direct correlation between treatment costs and two variables: appearance of neck nodal metastases and complex reconstructive surgical procedures. This finding was in line with a recent paper by Porta-Vázquez et al. (2023), who reported that costs for diagnostic and therapeutic procedures were determined by the ASA grade, tumor size, lymph node infiltration, and presence of metastases. Pollaers et al. (2019) and Polesel et al. (2019) also identified the development of local recurrences as a significant cost predictor. The presence of nodal metastasis is a well-recognized independent predictor of survival (de Bree et al., 2000) and is usually closely related (spatially and chronologically) to the related squamous cell carcinoma (Morandi et al., 2015).

Thus, there is an urgent need to identify novel techniques and technologies that can reduce locoregional recurrence rates in oral cancer patients, not only for the survival of these patients but also to reduce the cost of illness. For example, different authors have proposed preoperative molecular markers to identify aggressive OSCCs and help surgeons plan the most appropriate treatment option (Gissi et al., 2020; Foschini et al., 2013; Tarsitano et al., 2016b; Ishibashi-Kanno et al., 2023; Pandya and Natarajan, 2023). Such information can be helpful when deciding on neck management for patients with cT1N0 OSCC, to identify patients at high risk of occult nodal metastases. Recently, there has been a trend towards 'personalized medicine', in which specific information about an individual patient is used to calculate predictive nomograms and optimize patient care. It is likely that these types of model will become increasingly important in the future in reducing the direct costs of treatment.

Finally, our study demonstrated that long and complex multimodal treatments, largely associated with advanced cancers, are associated with higher costs. Although costs should not drive decisions relating to oral cancer treatment, to the disadvantage of patient survival and prognosis, new technologies must be sustainable in the economic field, because healthcare systems do not have unlimited resources.

Our study had some limitations. First, our data came from the records of a small cohort of patients from a single institution, and may not be representative of all regions in Italy. However, our study population was in line with the existing literature in terms of staging at diagnosis and locoregional recurrences rates, while the calculated cost of treatment was also in agreement. Second, our study reported only the direct costs of oral cancer treatment. As reported by several authors (Pollaers

et al., 2019; Zavras et al., 2002; Polesel et al., 2019; Lairson et al., 2017), oral cancer treatment is associated with many indirect costs (reduced productivity, loss of income, costs of comorbidities, reduction in life years, and reduction in quality of life), which should also be considered, and therefore direct costs underestimate the true cost of the disease.

5. Conclusion

Our study confirmed that an early diagnosis and a personalized preoperative OSCC treatment aimed at reducing the risk of locoregional recurrence may have a fundamental role in the reduction of healthcare costs, and in improvement of the quality of life of patients with OSCC. Cost reduction strategies should focus on the development of diagnostic and prognostic aids that can correctly identify patients at high risk of OSCC development, and thus determine the most appropriate treatment options according to the patient's risk profile before index tumor resection.

Declaration of competing interest

All authors have no conflicts of interest to declare.

References

Amin, M.B., Edge, S., Greene, F., Byrd, D.R., Brookland, R.K., Washington, M.K., Gershenwald, J.E., Compton, C.C., Hess, K.R., Sullivan, D.C., Jessup, J.M., Brierley, J.D., Gaspar, L.E., Schilsky, R.L., Balch, C.M., Winchester, D.P., Asare, E.A., Madera, M., Gress, D.M., Meyer, L.R. (Eds.), 2017. AJCC Cancer Staging Manual, eighth ed. Springer International Publishing, Germany.

AIOM (Associazione Italiana di Oncologia Medica). I numeri del cancro in Italia. Accessed in 2023. https://www.aiom.it/i-numeri-del-cancro-in-italia.

Brocklehurst, P., Kujan, O., O'Malley, L.A., Ogden, G., Shepherd, S., Glenny, A.M., 2013. Screening programmes for the early detection and prevention of oral cancer. Cochrane Database Syst. Rev. CD004150, 2013.

Brocklehurst, P.R., Speight, P.M., 2018. Screening for mouth cancer: the pros and cons of a national programme. Br. Dent. J. 225, 815–819.

Caudell, J.J., Gillison, M.L., Maghami, E., Spencer, S., Pfister, D.G., Adkins, D., Birkeland, A.C., Brizel, D.M., Busse, P.M., Cmelak, A.J., Colevas, A.D., Eisele, D.W., Galloway, T., Geiger, J.L., Haddad, R.I., Hicks, W.L., Hitchcock, Y.J., Jimeno, A., Leizman, D., Mell, L.K., Mittal, B.B., Pinto, H.A., Rocco, J.W., Rodriguez, C.P., Savvides, P.S., Schwartz, D., Shah, J.P., Sher, D., St John, M., Weber, R.S., Weinstein, G., Worden, F., Yang Bruce, J., Yom, S.S., Zhen, W., Burns, J.L., Darlow, S.D., 2022. NCCN Guidelines® Insights: head and neck cancers, version 1.2022. J. Natl. Compr. Cancer Netw. 20, 224–234.

de Bree, R., Deurloo, E.E., Snow, G.B., Leemans, C.R., 2000. Screening for distant metastases in patients with head and neck cancer. Laryngoscope 110, 397–401.

Epstein, J.D., Knight, T.K., Epstein, J.B., Bride, M.A., Nichol, M.B., 2008. Cost of care for early- and late-stage oral and pharyngeal cancer in the California Medicaid population. Head Neck 30, 178–186.

Foschini, M.P., Leonardi, E., Eusebi, L.H., Farnedi, A., Poli, T., Tarsitano, A., Cocchi, R., Marchetti, C., Gentile, L., Sesenna, E., Marucci, G., Montebugnoli, L., 2013. Podoplanin and E-cadherin expression in preoperative incisional biopsies of oral squamous cell carcinoma is related to lymph node metastases. Int. J. Surg. Pathol. 21, 133–141.

Giovannacci, I., Vescovi, P., Manfredi, M., Meleti, M., 2016. Non-invasive visual tools for diagnosis of oral cancer and dysplasia: a systematic review. Med. Oral Patol. Oral Cir. Bucal 21, e305–e315.

Gissi, D.B., Fabbri, V.P., Gabusi, A., Lenzi, J., Morandi, L., Melotti, S., Asioli, S., Tarsitano, A., Balbi, T., Marchetti, C., Montebugnoli, L., 2020. Pre-operative evaluation of DNA methylation profile in oral squamous cell carcinoma can predict tumor aggressive potential. Int. J. Mol. Sci. 21, 6691.

Gissi, D.B., Morandi, L., Colella, G., De Luca, R., Campisi, G., Mauceri, R., Romeo, U., Tenore, G., Mignogna, M.D., Adamo, D., Oteri, G., Marcianò, A., Vescovi, P., Meleti, M., Serpico, R., Di Stasio, D., Pentenero, M., Santarelli, A., Bianchi, A., Crimi, S., Marchetti, C., Tarsitano, A., Foschini, M.P., Montebugnoli, L., 2021.

Clinical validation of 13-gene DNA methylation analysis in oral brushing samples for detection of oral carcinoma: Italian multicenter study. Head Neck 43, 1563–1573.

Huang, S.Y., Chen, H.M., Liao, K.H., Ko, B.S., Hsiao, F.Y., 2020. Economic burden of cancers in Taiwan: a direct and indirect cost estimate for 2007–2017. BMJ Open 10, e036341.

Hussaini, S.M.Q., Gupta, A., Dusetzina, S.B., 2022. Financial toxicity of cancer treatment. JAMA Oncol. 8, 788.

Ishibashi-Kanno, N., Yamagata, K., Hara, T., Takaoka, S., Fukuzawa, S., Uchida, F., Bukawa, H., 2023. Prognostic prediction using maximum standardized uptake value ratio of lymph node-to-primary tumor in preoperative PET-CT for oral squamous cell carcinoma. J Stomatol Oral Maxillofac Surg 124, 101489.

Kademani, D., Bell, R.B., Bagheri, S., Holmgren, E., Dierks, E., Potter, B., Homer, L., 2005. Prognostic factors in intraoral squamous cell carcinoma: the influence of histologic grade. J. Oral Maxillofac. Surg. 63, 1599–1605.

Kim, K., Amonkar, M.M., Högberg, D., Kasteng, F., 2011. Economic burden of resected squamous cell carcinoma of the head and neck in an incident cohort of patients in the UK. Head Neck Oncol. 3, 47.

Lairson, D.R., Wu, C.F., Chan, W., Dahlstrom, K.R., Tam, S., Sturgis, E.M., 2017. Medical care cost of oropharyngeal cancer among Texas patients. Cancer Epidemiol. Biomarkers Prev. 26, 1443–1449.

Milani, V., Zara, A.L.S.A., da Silva, E.N., Cardoso, L.B., Curado, M.P., Ribeiro-Rotta, R.F., 2021. Direct healthcare costs of lip, oral cavity and oropharyngeal cancer in Brazil. PLoS One 16, e0246475.

Morandi, L., Tarsitano, A., Gissi, D., Leonardi, E., Balbi, T., Marchetti, C., Montebugnoli, L., Foschini, M.P., 2015. Clonality analysis in primary oral squamous cell carcinoma and related lymph-node metastasis revealed by TP53 and mitochondrial DNA next generation sequencing analysis. J. Cranio-Maxillo-Fac. Surg. 43, 208–213.

Morikawa, T., Shibahara, T., Nomura, T., Katakura, A., Takano, M., 2020. Non-invasive early detection of oral cancers using fluorescence visualization with optical instruments. Cancers 12, 2771.

Nijdam, W., Levendag, P., Noever, I., Uyl-de Groot, C., van Agthoven, M., 2004. Cost analysis comparing brachytherapy versus surgery for primary carcinoma of the tonsillar fossa and/or soft palate. Int. J. Radiat. Oncol. Biol. Phys. 59, 488–494.

Pandya, J.A., Natarajan, S., 2023. A study on histological grading systems of oral squamous cell carcinoma and comparison of their efficacy in determining the nature (clinical and histopathological) and prognosis of oral squamous cell carcinoma. J. Cancer Res. Therapeut. 19, S198–S205.

Polesel, J., Lupato, V., Collarile, P., Vaccher, E., Fanetti, G., Giacomarra, V., Palazzari, E., Furlan, C., Matrone, F., Navarria, F., Gobitti, C., Minatel, E., Serraino, D., Birri, S., Franchin, G., 2019. Direct health-care cost of head and neck cancers: a population-based study in north-eastern Italy. Med. Oncol. 36, 31.

Pollaers, K., Massingham, I., Friedland, P.L., Farah, C.S., 2019. The economic burden of oral squamous cell carcinoma in Australia. J. Oral Pathol. Med. 48, 588–594.

Porta-Vázquez, M., López-Cedrún, J.L., Fernández-Sanromán, J., García-Mato, E., Diz-Dios, P., Diniz-Freitas, M., 2023. Estimating the direct costs of oral cancer in Spain: a retrospective hospital data analysis. Med. Oral Patol. Oral Cir. Bucal 28, e425–e432.

Raman, S., Shafie, A.A., Tan, B.Y., Abraham, M.T., Chen Kiong, S., Cheong, S.C., 2023. Economic evaluation of oral cancer screening programs: review of outcomes and study designs. Healthcare 11, 1198.

Rezapour, A., Jahangiri, R., Olyaeemanesh, A., Kalaghchi, B., Nouhi, M., Nahvijou, A., 2018. The economic burden of oral cancer in Iran. PLoS One 13, e0203059.

Ribeiro-Rotta, R.F., Rosa, E.A., Milani, V., Dias, N.R., Masterson, D., da Silva, E.N., Zara, A.L.S.A., 2022. The cost of oral cancer: a systematic review. PLoS One 17, e0266346.

Singh, A.G., Chaukar, D., Gupta, S., Pramesh, C.S., Sullivan, R., Chaturvedi, P., Badwe, R., 2021. A prospective study to determine the cost of illness for oral cancer in India. Ecancermedicalscience 15, 1252.

Sung, H., Ferlay, J., Siegel, R.L., Laversanne, M., Soerjomataram, I., Jemal, A., Bray, F., 2021. Global Cancer Statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. Ca - Cancer J. Clin. 71, 209–249.

SEER (Surveillance, Epidemiology, and End Results). Cancer of the oral cavity and pharynx — cancer stat facts. Accessed September 2023. https://seer.cancer.gov/stat facts/html/oralcav.html.

Tarsitano, A., Battaglia, S., Crimi, S., Ciocca, L., Scotti, R., Marchetti, C., 2016a. Is a computer-assisted design and computer-assisted manufacturing method for mandibular reconstruction economically viable? J. Cranio-Maxillo-Fac. Surg. 44, 795–799.

Tarsitano, A., Asioli, S., Morandi, L., Monti, V., Righi, A., Morselli Labate, A.M., Nardi, E., Foschini, M.P., Marchetti, C., 2016b. Laminin-5 and insulin-like growth factor-II mRNA binding protein-3 (IMP3) expression in preoperative biopsy specimens from oral cancer patients: their role in neural spread risk and survival stratification. J. Cranio-Maxillo-Fac. Surg. 44, 1896–1902.

van Agthoven, M., van Ineveld, B.M., de Boer, M.F., Leemans, C.R., Knegt, P.P., Snow, G. B., Uyl-de Groot, C.A., 2001. The costs of head and neck oncology: primary tumours, recurrent tumours and long-term follow-up. Eur. J. Cancer 37, 2204–2211.

Wissinger, E., Griebsch, I., Lungershausen, J., Foster, T., Pashos, C.L., 2014. The economic burden of head and neck cancer: a systematic literature review. Pharmacoeconomics 32, 865–882.

Zavras, A., Andreopoulos, N., Katsikeris, N., Zavras, D., Cartsos, V., Vamvakidis, A., 2002. Oral cancer treatment costs in Greece and the effect of advanced disease. BMC Publ. Health 2, 12.