Prognostic indicators of improved survival and quality of life in surgically treated oral cancer

Giancarlo Tirelli, MD,[a] Annalisa Gatto, MD,[a] Pierluigi Bonini, MD,[a] Margherita Tofanelli, MD,[a] Zoran M. Arnež, MD, PhD,[b] and Alice Piccinato, MD[a]

Objective. No published study has analyzed the prognostic factors of surgically treated oral squamous cell carcinoma (OSCC) in relation to both survival and quality of life (QoL). The aim of this study was to analyze postoperative QoL in relation to survival to identify which parameters can predict the long-term outcome allowing the best QoL.

Study Design. This retrospective cohort study considered 167 patients affected by OSCC treated surgically at the Otolaryngology Department of Cattinara Hospital (Trieste, Italy) by a single surgeon. We collected data about the main prognostic factors and the postoperative QoL 12 month after surgery.

Results. The 5-year overall survival rate was equal to 68.1%, and the 5-year disease-specific survival was 77.8%. In this sample, 32% of patients also underwent adjuvant chemoradiotherapy. On stepwise Cox regression, the best predictors of disease-specific survival were the N stage ($P < .001$) and tumor depth of invasion ($P < .001$). QoL was affected by N stage, depth of invasion, invasive surgical approach, radiotherapy, and neck dissection ($P < .05$).

Conclusion. The prognostic factors that affect both survival rates and residual QoL are the surgical approach, the neck stage, and the depth of invasion, all of which can be minimized by early diagnosis.

Head and neck cancer is the sixth most common human cancer, accounting for 3% of all cancers.[1] The most common localization is the oral cavity, and 90% of these cases are oral squamous cell carcinomas (OSCC).[2] The worldwide estimated incidence is around 275,000 new cases every year, and the 5-year survival rate in most countries is approximately 50%.[3]

OSCC is characterized by a poor prognosis and a low overall survival (OS) rate despite sophisticated surgical and radiotherapy treatment modalities.[4-6] However, because OS describes the general survival of OSCC patients but fails to consider the influence of age, comorbidity, lifestyle, and background, it is preferable to use the more accurate disease-specific survival (DSS).

Over the past 30 years, the survival of patients with OSCC has improved largely as a result of a better understanding of the biology of local progression, early identification and treatment of metastatic lymph nodes in the neck, and use of adjuvant postoperative radiotherapy or chemoradiotherapy.[7] Surgery has long been the most well-established and accepted approach for the treatment of the majority of OSCC.[7,8]

Therapeutic decision making is currently based on clinical tumor staging supplemented with conventional histopathologic grading. This has, however, been reported to be an imperfect prognostic indicator,[9,10] with clinicians requiring new diagnostic tools to help them tailor management to the individual patient's needs.[9] The head and neck region is central to several essential functions such as speech, breathing, and feeding, and cancers in this region might be expected to have severe effects on day-to-day living.[11] Evaluation of the patients' quality of life (QoL) can measure the impact of both the disease and the treatment on a patient's life, thereby acting as a prognostic indicator of future outcomes.[12-17] In the past, OS was the only factor used to estimate the failure of oncologic management, whereas nowadays it is essential to consider not only how long patients survive after surgery but also how gratifying their postoperative life is.[18-20] The literature provides many different questionnaires devised to evaluate the subjective QoL of patients and allow a better estimate of treatment outcomes.

In parallel, many different prognostic factors have been proposed with the aim of identifying which potential parameters could influence patients' OS and DSS. Janot et al.[21] introduced a classification that divides the prognostic factors of OSCC into patient-, tumor-, and treatment-related factors. No published study has analyzed the prognostic factors of surgically treated OSCC in relation to both survival and QoL. The aim of this study was to analyze postoperative QoL in relation to overall and disease-specific survival to identify which

[a]ENT Clinic, Head and Neck Department, Azienda Sanitaria Universitaria Integrata di Trieste, Italy.

[b]Department of Plastic and Reconstructive Surgery, Azienda Sanitaria Universitaria Integrata di Trieste, Trieste, Italy.

Aaccepted for publication Jan 23, 2018.

Statement of Clinical Relevance

There is no published study analyzing the prognostic factors of surgically treated squamous cell oral cancer in relation to both survival and quality of life even if these 2 factors are requested as the most relevant by the patients.

parameters can predict the long-term outcome allowing the best QoL.

METHODS

In this retrospective cohort study, we collected data about 167 patients affected by OSCC who underwent primary surgery carried out by the same medical team from May 2003 to June 2012 at the Otolaryngology Department of Cattinara Hospital (University of Trieste, Italy). Exclusion criteria were neoadjuvant radiotherapy as first choice treatment, histologic type other than OSCC, and advanced stage considered as unresectable disease or unfit for surgery according to the most recent international guidelines.[22] Patients were informed about the purpose of the study and gave their consent for the anonymous use of their data.

Surgical protocols

The choice of therapeutic option was based on the National Comprehensive Cancer Network (NCCN) guidelines.[22]

With regard to surgery, the transoral approach was generally performed when no microvascular flap reconstruction was needed; the pull-through operation was used to control tumors with deep extension into the tongue and floor of the mouth but without invasion of the jaw; a conservative transmandibular approach with a mandibulotomy was reserved for tumors that could not be reached by any other approach. When there was minimal invasion of the jaw, marginal mandibulectomy was done, whereas lesions infiltrating the bone marrow were treated with segmental mandibulectomy. Primary closure was performed after partial glossectomy, hemiglossectomy, or superficial resection of the cheek. Either no reconstruction was performed or a Thiersch graft was placed after resection of superficial tumors of the floor of the mouth; microvascular flaps were used for reconstruction in the event of mylohyoid muscle invasion, deep resection of the cheek or resection of the hard palate. In selected cases, the hard palate defect was managed by placing an obturator prosthesis. No reconstruction was performed after marginal mandibulectomy, whereas a peroneal flap was used in the event of segmental mandibulectomy.

Clinically N0 necks (cN0) with a tumor depth of invasion (DOI) less than 2 mm did not undergo neck dissection but were managed with a "wait and see" approach. If the tumor had a DOI from 2 mm to 4 mm, performance of the neck dissection depended on tumor grading. We observed well- or moderately differentiated, highly or moderately keratinized T1 stages; poorly or not differentiated T2 stages with low keratinization underwent neck dissection. When tumor DOI was greater than 4 mm, a supraomohyoid neck dissection (level I-III) was done, and when the tumor crossed the midline, a bilateral dissection was performed. No sentinel node biopsy was performed.

In cN+ necks, we performed a selective neck dissection (level I-IV) or a modified radical neck dissection (I-V). The latter was chosen when likelihood of extracapsular spread (ECS) was preoperatively considered high, basing the prediction on clinical and radiologic features according to literature: advanced stages of N category, lymph node greater than 2 cm in a single dimension, irregular borders, presence of necrosis, adjacent tissue involvement, and level 4 or 5 adenopathy.[23,24]

Postoperative radiotherapy was recommended according to NCCN guidelines as follows: ECS, positive resection margins, pT4 or pT3 primary, pN2 or pN3 nodal disease, nodal disease in levels IV or V, perineural invasion, or vascular embolism.

Follow-up

Oncologic follow-up visits were scheduled according to the NCCN guidelines: monthly during the first year, bimonthly during the second year, and every 4 to 6 months from the third to the fifth year after surgery.

Data collection

This study analyzed the correlation between prognostic factors and both OS and DSS. The prognostic factors were divided into patient-related, tumor-related, and treatment-related factors. Postoperative QoL was assessed by means of a questionnaire, and the scores were correlated both to OS and to DSS.

The prognostic factors considered were as follows:

1. Patient-related: Sex and age of the patient. Because age was considered a binary variable, the sample was divided into 2 groups, one of younger patients and one of older patients (cutoff point, 75 years).
2. Tumor-related: The site and stage of the tumor. T1 and T2 tumors were classified as initial stage and T3 and T4 as advanced stage. The histopathologic reports were reviewed to record ECS in the cervical lymph nodes and tumor DOI, considering 5 mm to be the cutoff between noninvasive and invasive lesions.[25]
3. Treatment-related: The surgical approach, neck dissection, the use of microvascular flaps, and adjuvant radiotherapy if any. The surgical approach was considered a binary variable: We distinguished between a conservative approach, when the integrity of the mandibular arch was preserved, and an invasive approach, when resection of the mandible was performed. We also recorded the timing and type of neck dissection associated with the tumor resection. We noted whether the patient underwent adjuvant radiotherapy when recommended by the NCCN guidelines.[22]

Finally, to evaluate QoL, each oncologic patient in our department routinely completes the University of Wash-

ington Quality of Life Questionnaire 6 and 12 months after surgery. In this study, we considered the 12-month questionnaire score only, because it better reflects a stabilized condition with consolidated surgical outcomes. The questionnaire is composed of 12 single-question items, which have between 3 and 6 possible responses scored evenly from 0 to 100. The domains investigate pain, appearance, activity, recreation, swallowing, chewing, speech, shoulder, taste, saliva, mood, and anxiety. There are also 4 global questions about overall QoL, in which patients are asked to consider not only physical and mental health but also other social factors. The final score is expressed as a percentage as result of a weighted average, where 0 corresponds to the worst QoL and 100 to the best.

Statistical analysis

Statistical analysis was performed using dedicated software (Statistical Package for Social Sciences Version 15, SPSS Inc., Chicago, IL, USA). Kaplan-Meier methods were used to estimate the DSS and OS for each group, and the log-rank test was used to compare the survival curves. Cox regression was applied to investigate the main independent predictors of survival. To correlate the statistically significant prognostic factors with the 12-month QoL scores, all parameters were converted into binary data and significance was tested with the Mann-Whitney test. Age was categorized in 3 subgroups (<65 years, 65-75 years, and >75 years) and we compared them using a Kruskal-Wallis test. The level of significance for all tests was $P < .05$.

RESULTS

In the 167 patients considered in this study, the 5-year OS rate was equal to 68.1% and the 5-year DSS rate was 77.8% (Figure 1). The QoL questionnaire was completed by 150 patients, there being 17 deaths during the first year of follow-up. The median time from surgery to the 12-month questionnaire was 13.2 months (interquartile ratio = 1.5).

Sex and age (63.8 ± 12.14 years) were not found to correlate significantly with either survival or QoL ($P > .05$).

The T stage did not correlate significantly with either DSS or QoL; only the difference between DSS of stages pT1 and pT4 proved to be significant ($P = .029$). On the contrary, T stage was statistically related with OS ($P = .006$). The N stage was statistically the most significant parameter for the OS ($P < .001$) and DSS ($P < .001$), which was 89.60% in pN0, 67.90% in pN1, 45.80% in pN2, and 55.60% in pN3; similarly, pN+ patients reported a significantly lower QoL scores ($P = .001$) (Figure 2). The percentage of occult metastases detected at histopathologic examination after elective neck dissection in patients classified as cN0 was 20.4%. The difference between the DSS in cN0 patients with a negative elective neck dissection (DSS = 89.6%) and cN0 patients with a positive elective neck dissection (DSS = 64%) was statistically significant ($P < .001$), and the OS had the same trend ($P < .001$). Likewise, the difference in QoL scores between these 2 subgroups was statistically significant ($P = .025$) (Figure 3). Advanced tumor stages had a significant worsening of survival and QoL ($P < .05$). Patients with a tumor DOI less than 5 mm had a DSS of 87.8%, those with a DOI greater than 5 mm had a DSS of 68.2% ($P = .001$). The difference in QoL between these 2 subgroups was also statistically significant ($P = .002$) (Figure 4). The presence of ECS (50% of

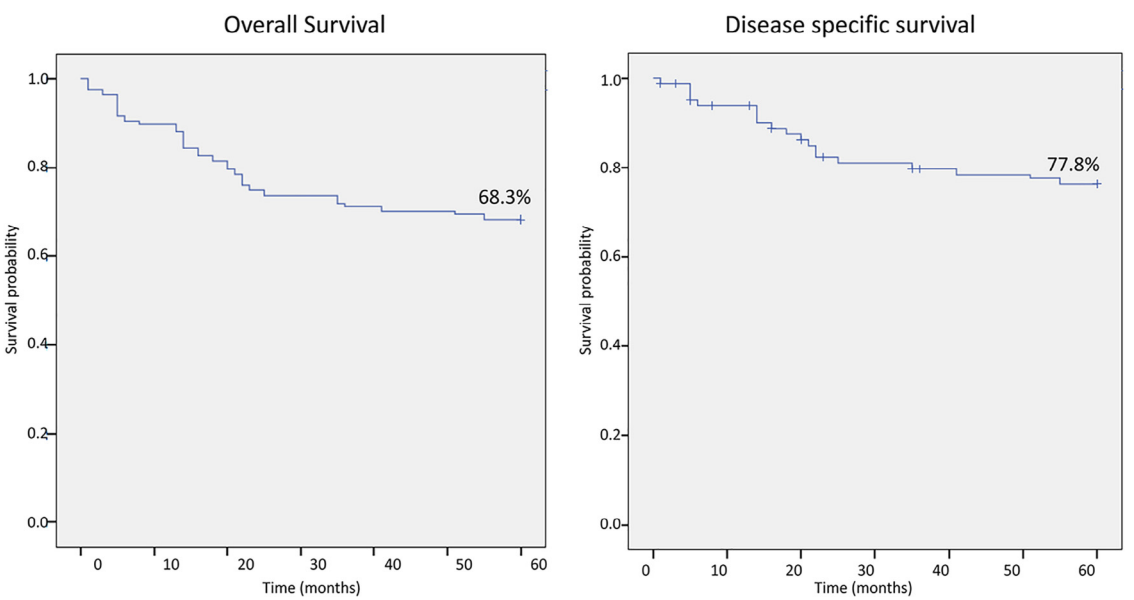

Fig. 1. Kaplan-Meier plots showing overall survival (OS) and disease-specific survival (DSS) and of the entire cohort.

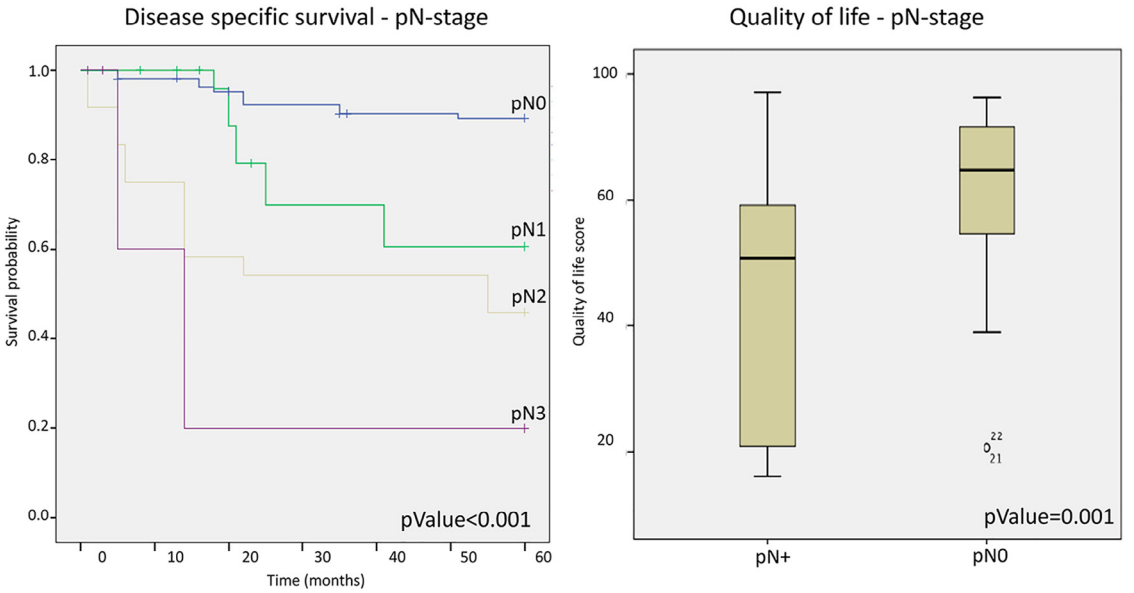

Fig. 2. Kaplan-Meier plot demonstrating disease-specific survival in relation to pathologic node (pN) stage and box and whiskers plot of quality-of-life (QoL) scores.

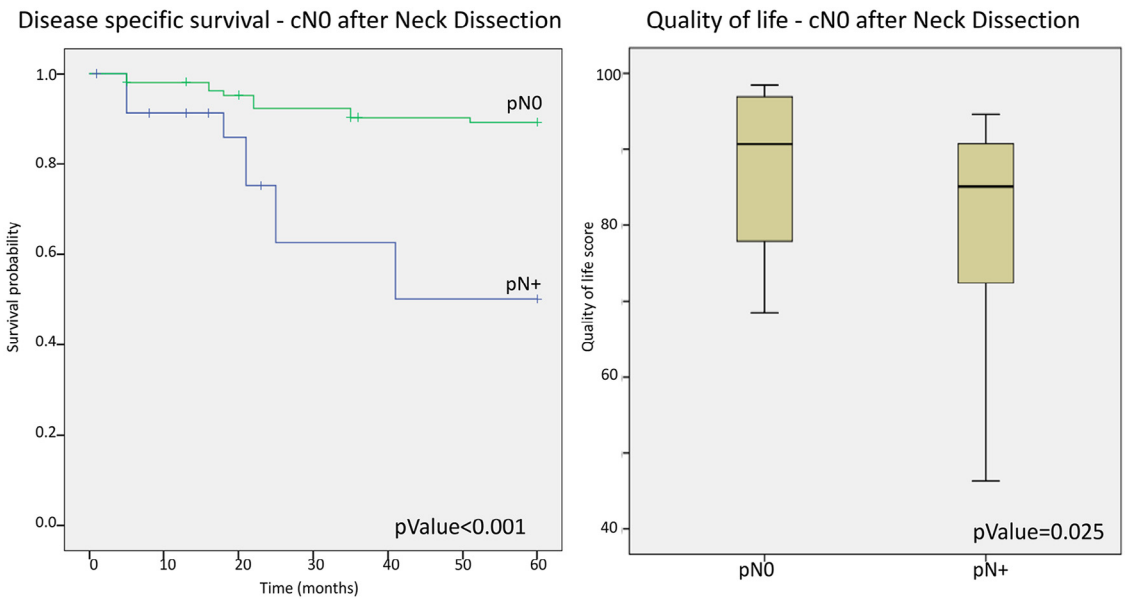

Fig. 3. Kaplan-Meier plot demonstrating disease-specific survival in relation to neck dissection and box and whiskers plot of quality-of-life (QoL) scores.

pN+ specimen) caused a decrease in DSS from 81.7% to 49.3% ($P = .004$).

Statistical analysis of the surgical approach had a significant relationship with both OS and DSS ($P = .001$ and $P < .001$, respectively). The difference in QoL between these subgroups was also significant ($P = .004$) (Figure 5). The patients who underwent microvascular flap reconstruction (anterolateral thigh flap, radial forearm free flap, or fibula flap) did not have worse OS, DSS, or QoL compared with patients treated without microvascular flap reconstruction.

Patients with clear margins at histopathologic examination had a DSS of 75.5%, which dropped to 63.8% when margins were positive ($P = .015$). Radiotherapy was not found to affect the survival rate, DSS values being 81.30% in patients who underwent radiotherapy and 76.50% in those who did not. Conversely, the QoL scores of patients who underwent radiotherapy were significantly lower than

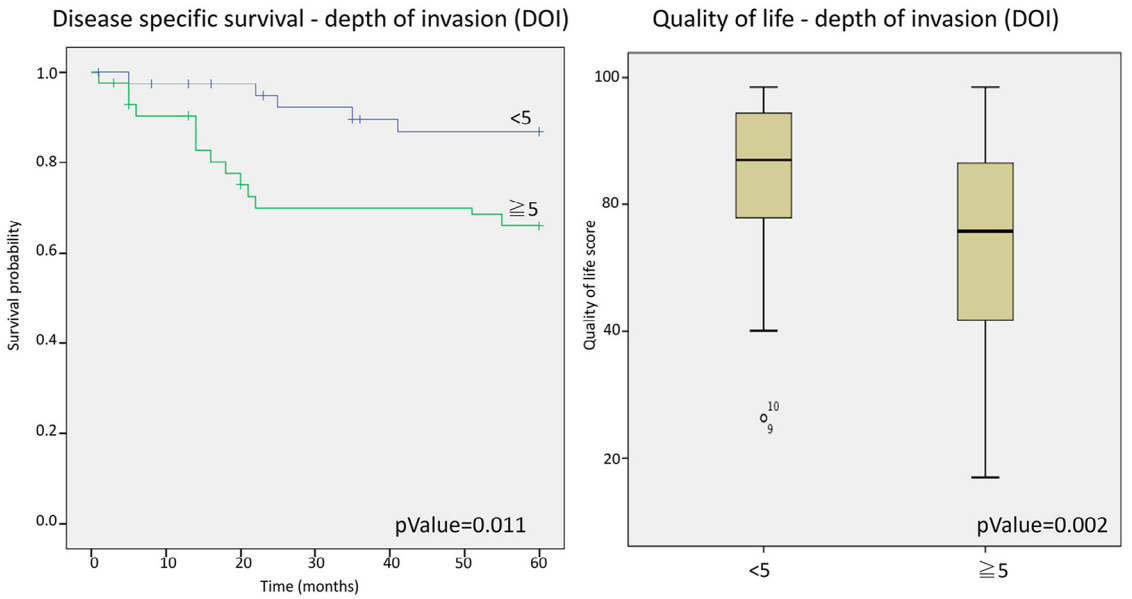

Fig. 4. Kaplan-Meier plot demonstrating disease-specific survival in relation to tumor depth of invasion (DOI) and box and whiskers plot of quality-of-life (QoL) scores.

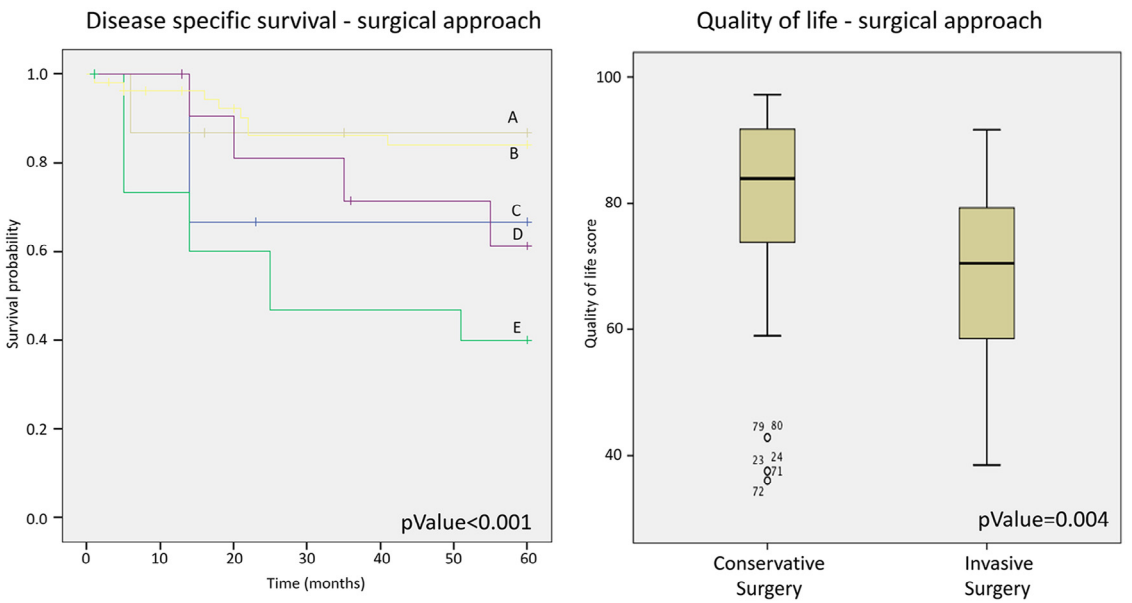

Fig. 5. Kaplan-Meier plot demonstrating disease-specific survival in relation to the surgical approach and box and whiskers plot of quality-of-life (QoL) scores. **(A)** Transoral surgery; **(B)** marginal mandibulectomy; **(C)** segmental mandibulectomy; **(D)** mandibulotomy; **(E)** pull-through. *Conservative surgery* includes transoral, pull-through, and mandibulotomy; *invasive surgery* includes marginal and segmental mandibulectomy.

those of patients who were not irradiated ($P = .012$) (Figure 5). Patients with a cN0 diagnosis who underwent neck dissection had a worse QoL (80.9%) than those who did not (88.2%) ($P = .025$), whereas the OS and DSS rates were similar in the 2 subgroups. The comparison between the different types of neck dissection indicated that QoL scores changed significantly ($P = .03$); in particular QoL was 77.2% after a supraomohyoid neck dissection, 74.1% after a selective neck dissection (I-IV), and 68.8% after a radical neck dissection (I-V). (Figure 6)

Cox regression modeling indicated that best predictors of DSS were the N stage ($P = .015$) and tumor DOI ($P = .048$). By multivariate analysis, N stage and tumor DOI were independent factors affecting DSS.

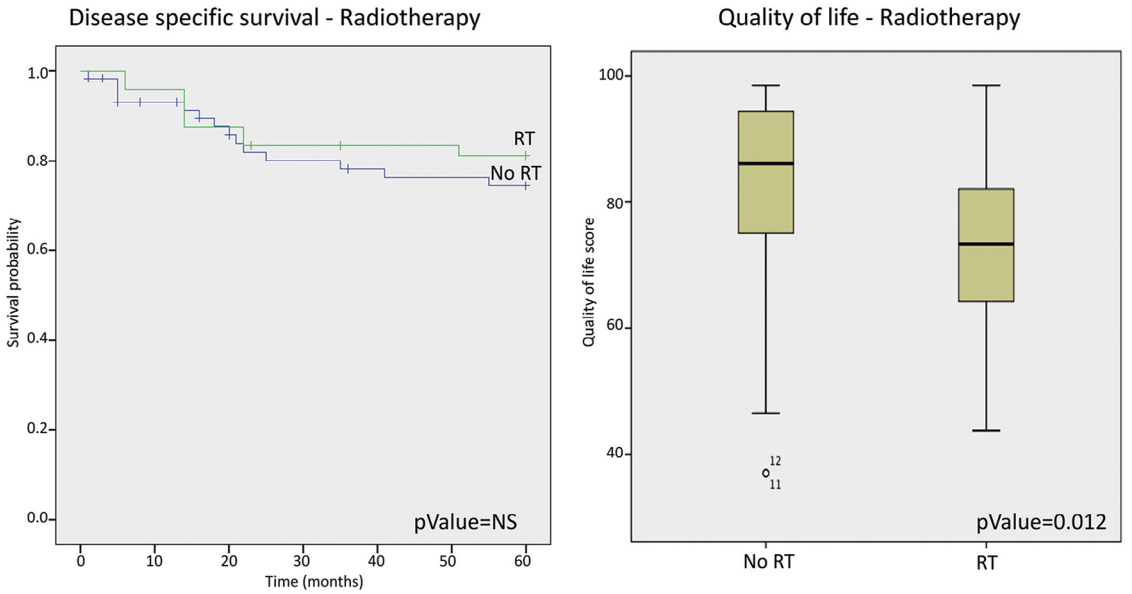

Fig. 6. Kaplan-Meier plot demonstrating disease-specific survival in relation to radiotherapy and box and whiskers plot of quality-of-life (QoL) scores.

Table I summarizes the characteristics of the sample and the results.

DISCUSSION

In the past, the aim of cancer treatment was to achieve surgical radicality irrespective of the patient's residual function. In recent years, by contrast, increasing attention has been paid to both postoperative well-being and the balance between oncologic and functional outcomes. As a consequence, OS is no longer the only outcome to be considered in head and neck oncology.

Our study found that several closely interrelated parameters affect survival rates: N stage, surgical approach, tumor DOI, ECS, and the presence of occult metastases in clinically negative cervical lymph nodes. The global DSS in our study was 77.7%. This promising result is higher than that reported in the literature,[26] and it is likely because of the prevalence of early stage tumors in our sample.

The T stage correlated with OS but did not with either DSS or QoL. Even though this could seem a contradiction, the stage of T is only a dimensional parameter, and several tumors classified as advanced stages have an exophytic growth that might not be associated with a parallel infiltrative growth. For this reason, they might not require an aggressive surgical approach with a consequent lower QoL. In fact, according to other studies, the DOI was found to be the main tumor invasion parameter to correlate with both survival[27] and QoL.

In relation to survival, most published studies have correlated OS separately with T and N stages.[28-34] Our data confirm the relationship between OS and N stage, which also proved to be the most influential parameter for DSS. In our opinion, this result emphasizes the focal role of neck treatment in disease control. Although neck treatment in the case of positive lymph nodes (cN+) is generally accepted, some controversy exists on the treatment of clinically negative necks (cN0). A prophylactic neck dissection is performed to avert the possible spread of an occult metastasis, a possibility that is reported to range between 20% to 30% and may reflect undertreatment.[35,36] On the other hand, to avoid this risk, 70% to 80% of patients would have to be overtreated, with a likely increase in surgical morbidity. Furthermore, neck dissection is associated with lower QoL scores, as reported in several studies[37-41] and also confirmed by our results. In particular, there were statistically significant differences between QoL and neck dissection type, confirming that more extensive surgery in the neck is associated with greater postoperative morbidity.[42] In our sample, there was no significant difference in survival rate between patients treated with prophylactic or delayed neck dissection, a finding consistent with several published studies.[43] By contrast, a recent study by Rogers et al.[26] and a Cochrane review[44] have highlighted the importance of prophylactic neck dissection because, although not actually increasing survival, its performance resulted in improved locoregional control. On the other hand, D'Cruz et al.[45] reported that elective neck dissection resulted in higher rates of overall and disease-free survival than did therapeutic neck dissection in cases of early-stage OSCC.

The decision as to which surgical approach to perform is based on several parameters, such as the T and N stage

Table I. Five-year overall survival (OS), disease-specific survival (DSS), and QOL

No. patients		*OS = 68.3%*	*DSS = 77.8%*	*QOL*
Gender		*P* = NS	*P* = NS	*P* = NS
Male	111	67.9%	78.9%	78.4
Female	56	69.0%	75.9%	83.8
Age		*P* = NS	*P* = NS	*P* = NS
<65	78	65.4%	76.3%	77.1
65-75	49	79.6%	85.7%	73.5
>75	40	60.0%	73.4%	74.8
T stage		*P* = .006	*P* = NS	*P* = NS
pT1	76	80.3%	84.2%	pT1-2 81.1
pT2	45	60.0%	71.1%	
pT3	21	71.4%	90.5%	pT3-4 77.4
pT4	25	44.0%	60.0%	
N stage		*P* < .001	*P* < .001	*P* = .001
pN0	106	84.4%	89.6%	pN0 84.8
pN1	28	46.6%	67.9%	
pN2	24	45.8%	45.8%	pN+70.8
pN3	9	11.1%	55.6%	
Depth of invasion (DOI)		*P* = .011	*P* = .001	*P* = .002
<5	81	76.8%	87.8%	84.0
≥5	86	60.0%	68.2%	72.6
Flaps		*P* = NS	*P* = NS	*P* = NS
Yes	97	63.9%	74.7%	81.4
No	70	72.6%	81.0%	79.2
RT		*P* = NS	*P* = NS	*P* = .012
Yes	53	75.0%	81.3%	81.8
No	114	65.5%	76.5%	72.8
ND in cN0		*P* < .001	*P* < .001	*P* = .025
pN0	106	84.0%	89.6%	87.1
pN+	25	32.0%	64.0%	80.6
Surgical approach		*P* = .001	*P* < .001	*P* = .004
Transoral	106	77.6%	85.0%	SurgA 82.9
Marginal mandibulectomy	8	73.3%	86.7%	
Pull-through	8	33.3%	66.7%	SurgB 72.8
Segmental mandibulectomy	24	54.5%	63.6%	
Mandibulotomy	21	35.3%	47.1%	

Tumor site	*% of patients*	*No. of patients*
Tongue	43.1%	72
Floor of the mouth	28.7%	48
Hard palate	3.6%	6
Retromolar trigone	10.2%	17
Cheek	14.4%	24

QOL, quality of life; *NS,* not specified; *SurgA,* conservative surgery (transoral approach, pull-through and mandibulotomy); *SurgB,* invasive surgery (marginal and segmental mandibulectomy).

and the site of the lesion. As noted earlier, advanced and infiltrative tumors require more extensive resections that entail greater morbidity, a greater chance of failure, and a higher risk of recurrences. Therefore, it is plausible that the surgical approach has a major effect on residual QoL (*P* = .004), OS (*P* = .001), and DSS (*P* < .001), which decreases when a destructive approach involving mandibular resection is required. Roger et al.[46,47] compared different transmandibular approaches, obtaining different QoL levels, with worse scores in patients treated with a segmental mandibular resection compared with those treated with a rim mandibular resection. Other studies underline that mandibular resection could affect masticatory ability, swallowing, and phonation[48]; however, our literature review failed to identify any studies comparing the outcomes of different surgical approaches over a 5-year follow-up to evaluate DSS.

In the cohort analyzed, the patients who underwent microvascular flap reconstruction did not have worse DSS or QoL compared with those in whom it was not required. This may be a consequence of the appropriate use of the surgical technique for the correct indication, only when no other reconstruction was possible.

With regard to adjuvant therapy, patients who underwent postoperative therapy had an additional loss of QoL, without any improvement in survival. The

reported relationship between the role of adjuvant therapy and survival rates is controversial, although there is no doubt that radiotherapy heavily affects residual QoL.[40,48-50] In the sample considered, patients who underwent combined treatment had lower scores on the University of Washington Quality of Life Questionnaire, especially as regards chewing and swallowing ability. Although some studies found combined therapy to be associated with improved survival rates,[26,51,52] others failed to find any advantage in survival.[53-55] This could reflect an appropriate use of adjuvant therapy in accordance with the indications. In fact, the aim of adjuvant therapy is to complete the curative intent of surgery in cases in which surgery alone is not enough. Therefore, it is reasonable that when surgery alone achieves adequate oncologic resection (i.e., clear margins), the results in terms of OS become comparable to the OS obtained after radiotherapy when this is indicated, given that the presence of involved margins highly affects survival.[26]

The American Joint Committee on Cancer has recently published the eighth edition of its staging system, which introduces some changes: DOI has been incorporated in oral cancer staging, and extranodal extension has been added to the lymph node category to improve the prognostic performance.[42] In more detail, tumors smaller than 2 cm with a DOI of 5 cm or less are staged as pT1; tumors smaller than 2 cm with a DOI between 5 and 10 mm or tumors between 2 and 4 cm and a DOI less than 10 mm are defined as pT2; tumors greater than 4 cm or with a DOI that exceeds 10 mm are categorized as pT3; if ECS is present in a single node less than 3 cm in diameter, tumors are staged as pN2 a; all other cases with ECS are classified as pN3 b.

Among the predictive factors known to affect survival rates, according to our statistical analysis as well, the histopathologic parameters DOI and ECS were inversely related to survival.

Tumor DOI is considered an indicator of potential lymph node involvement,[56] and the literature correlates this value with shorter survival,[27,57] as also found in our sample. In fact, patients with a tumor DOI ≥5 mm had significantly lower QoL scores compared with those with DOI <5 mm, which is a consequence of the fact that tumors with a DOI ≥5 mm require a more aggressive treatment with a transmandibular approach, although there is no similar experience reported in the literature. ECS also correlated with decreased survival rates, confirming that the neck stage is an important parameter affecting the survival of patients with oral cancer.[26,33,51] The spread of occult metastasis as a possible consequence of undertreatment and ECS can reduce DSS, whereas QoL is affected by adjuvant therapy and the performance of elective neck dissection in patients with clinically negative necks (cN0).

Based on these results, our study confirms that treatment of the neck is a crucial step in the management of OSCC and that an early diagnosis is a fundamental goal. In the management of patients with cN0 necks, whether to treat surgically or to opt for a wait-and-see approach remains an open question. Therefore, it is reasonable to expect that patients who undergo a neck dissection will have a lower QoL than those who are monitored; in the latter case, the greater risk of developing a metastasis entails a higher risk of worse survival rates.

The main limit of this study is its retrospective design. However, our intent was to identify the prognostic correlates of better survival rates and higher QoL scores, so as to allow their further investigation by future prospective studies.

CONCLUSION

The factors that significantly influence DSS in our series are neck stage, DOI, surgical approach, and elective neck dissection, whereas those that affect QoL are neck stage, DOI, adjuvant radiotherapy, and surgical approach.

In conclusion, our study found that the prognostic factors that significantly influence both survival and residual QoL in OSCC patients are the surgical approach, the N category, and the tumor DOI. All of these factors are influenced by an early diagnosis, which proves to be crucial for the success of therapy in terms of both prognosis and QoL in oral cancer.

ACKNOWLEDGMENTS

The authors thank Itala Mary Ann Brancaleone, MA, RSA Dip TEFLA, teacher of Medical English at the University of Trieste, for her support in editing the manuscript.

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