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ORIGINAL ARTICLE

Long-term outcomes, quality of life, and costs of treatment modalities for T1–T2 lip carcinomas

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Abstract

Purpose: Early stage lip squamous cell carcinoma (lip SCC) can be treated with conventional excision, Mohs micrographic surgery (MMS), or brachytherapy. The aim of this retrospective study was to describe the medical outcomes, patient-reported outcomes, and costs of these treatments.

Methods: A retrospective cohort study of T1–T2 lip SSCs treated between 1996 and 2019. Medical outcomes, recurrences, and survival were retrieved from medical records. Facial appearance, facial function, and Quality of Life (QoL) were measured with the Face-Q H&N and EQ-5D-5L questionnaires. Costs were also calculated.

Results: Of the 336 lip SCCs, 122 were treated with excision, 139 with MMS, and 75 with brachytherapy. Locally, the recurrence rate was 2.7% and regionally 4.8%. There were 2% disease-related deaths. T2-stage and poor tumor differentiation were associated with recurrences. Posttreatment QoL, facial function, and appearance were rated as good. Brachytherapy was the most expensive treatment modality.

Conclusion: Early-stage lip SCC has a good prognosis, with a disease-specific survival of 98.2% after a median follow-up of 36 months, there was a high QoL and satisfaction at long-term follow-up. Based on the costs and the risk of locoregional recurrences, we believe that, for most noncomplex lip SCCs, MMS would be the most logical treatment option.

KEYWORDS
brachytherapy, conventional surgery, costs, lip carcinoma, management, Mohs micrographic surgery, quality of life, T1, T2

1 | INTRODUCTION

Carcinoma of the lip (lip SCC) is a type of skin cancer that, in terms of classification, falls within the head and neck area, with an incidence of approximately 150 new cases annually in the Netherlands (Dutch Cancer Registration "Nederlandse Kankerregistratie (NKR)"). Squamous cell carcinoma (SCC) is the most frequently reported type of lip cancer (95%), the majority arising at the vermilion border of the lower lip (de Visscher et al., 1998). Known risk factors are cumulative exposure to sunlight and long-term tobacco or alcohol consumption (de Visscher et al., 1998; Moore et al., 1999; Perea-Milla López et al., 2003). Males are more frequently affected,

with reported ratios between 9:1 and 6:1 (Biasoli et al., 2016; Han et al., 2016; Tseng et al., 2017). SSCs of the lip are usually detected at an early stage as the lesions are often visible and symptomatic (de Visscher et al., 2002; Han et al., 2016). As a result, lip SCC is one of the most curable malignancies in the head and neck region, with 5-year survival rates between 83% and 96% recorded (Hasson, 2008; Unsal et al., 2018; Zitsch, 1993). Early stage (T1–T2) lip SCCs are even associated with cure rates approaching 100% (Holmkvist & Roenigk, 1998; Mohs & Snow, 1985). Nevertheless, SCCs of the lip tend to metastasize more often (3.5%–11%) than other cutaneous SCCs (0.3%–0.6%) (Agostini et al., 2017; Kristensen et al., 2017; Rowe et al., 1992).

The upper and lower lips form a distinct anatomic unit that plays an important role in facial appearance and function, including eating, drinking, talking, and smiling (Casal et al., 2010; Hofer & Mureau, 2009). Lip cancer and the subsequent treatment can therefore play a major role in patients' quality of life (QoL) (Schüller et al., 2015). The most frequent treatments are conventional excision, Mohs micrographic surgery (MMS), and brachytherapy. Each treatment option has advantages and disadvantages. Conventional excision directly eradicates the tumor in a single-stage procedure but requires the application of safety margins, with a potentially higher risk of a negative functional and cosmetic impact, and only limited assessment of the excised margins (de Visscher et al., 2002). In contrast, MMS only requires narrow margins because of the immediate and complete assessment of the margins by frozen section slides during surgery (Mohs & Snow, 1985; Zide & Adnot, 1997). A disadvantage of MMS is that it can be time-consuming when it involves multiple stages and is more expensive than conventional excision due to the specialized training and equipment required (Hasson, 2008; van Leeuwen et al., 2015). Furthermore, MMS is only available in specialized institutes. As an alternative to surgery, brachytherapy can be considered, which can reduce the need to remove functional tissue in this anatomically important unit. However, the disadvantages of brachytherapy are that it requires hospital admission for multiple days, with general anesthesia in some cases, the radiotherapy can affect surrounding healthy tissue, and there can be radiation complications (Levendag et al., 2006; Rio et al., 2013).

Our institute (Erasmus Cancer Institute Rotterdam), a specialized tertiary medical center for skin cancer, patients with early stage lip SCC are treated by different specialists including dermatologists, radiation oncologists, plastic surgeons, and head and neck surgeons. The treatment choice is typically determined following a collaborative decision-making process involving the patient and consultation with the multidisciplinary team. Nevertheless, the preferences of the specialist who informed the patient about treatment options may also influence the eventual treatment. The costs are likely to vary as the required equipment, the length of treatment, and the hospital stay differ among the treatment modalities.

This study has aimed to investigate the long-term outcomes of the treatment of early stage (T1–T2) lip SCC at our institute. Survival and recurrence rates as well as patient-reported outcomes concerning facial appearance, facial function, and QoL were assessed. In addition, costs were calculated for each treatment modality.

2 | MATERIALS AND METHODS

2.1 | Setting and patients

Patients were considered eligible for inclusion in the study if they had a histologically confirmed T1–T2 lip SCC and were treated at the Erasmus MC Cancer Institute between 1996 and 2019. SCCs at the dry vermilion or cutaneous part of the lip, with N0 and M0 according to the AJCC 7 TNM classification, were included (Sobin et al., 2009). Intraoral SCCs, including those located at the wet vermillion, were excluded. We identified patients through PALGA, the nationwide histopathology and cytopathology data network in the Netherlands (Casparie et al., 2007). This database was combined with a database from the pathology department of the Erasmus MC. Additional patient and treatment characteristics, and medical outcomes, were obtained from medical patient records. The Dutch personal records database was consulted to evaluate which patients were still alive at the time of the analysis. The present study was conducted and reported according to the guidelines elaborated in the STROBE statement (Strengthening the Reporting of Observational Studies in Epidemiology) (von Elm et al., 2007).

Patients were excluded if they had received external radiotherapy, a neck dissection, or where there were insufficient data in their medical records. In terms of excision margins, the following definitions were used: (1) an inadequate margin was defined as tumor presence in any of the resection lines and (2) a close margin was considered to be present when the tumor was less than 2 mm from the resection line. Both medical records and all nationally available pathology records (PALGA) were screened to evaluate whether patients had a recurrence of the disease (local, regional, or distant metastasis). A local recurrent tumor was defined as a lip SCC at the same location within 2 years of the initial treatment whereas, if patients had a lip SCC more than 2 years after initial treatment, this was considered a secondary primary tumor. The 2-year cutoff mark was not applied in determining regional recurrences. Recurrence-free period was measured from the last day of treatment until the recurrence or to the last known day alive determined from the Dutch personal records database, whichever came first. The Medical Ethical Committee concluded that the Research Involving Human Subjects Act was not applicable to this study (MEC-2020-0391).

2.2 | Patient-reported outcome measures

Standardized and validated patient-reported outcome measures (PROMs) were assessed at the long-term follow-up review (>2 years after treatment). Patient satisfaction with facial appearance, facial function, and QoL was measured with the *Face-Q Head and Neck Cancer Module* (Cracchiolo et al., 2019). This PROM contains

multiple scales measuring satisfaction with facial appearance, eating and drinking, oral competence, smiling, and speaking. Furthermore, it measures the disease-specific QoL by assessing appearance-related distress, cancer worry, and distress about drooling, eating, smiling, or speaking. Each subdomain's score is on a scale from 1 to 100, with higher scores indicating better function or greater satisfaction. It has previously been shown to have good reliability with a Cronbach alpha coefficient of >0.87 for all scales and for test–retest between 0.86 and 0.96 (Cracchiolo et al., 2019). Where applicable, questions were added to evaluate if a patient's denture still fitted after the intervention or if a new denture was needed.

Health-related QoL (HR-QoL) was measured with the *EQ5D-5L* instrument, a preference-based 5-item questionnaire about mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each domain is scored from 1 = "no problems" to 5 = "extreme difficulty or inability." An EQ-5D summary index is calculated by applying a formula that attaches weights to each level in each dimension. This index score can range from −0.446 to 1, with 0, 1, and negative values corresponding, respectively, to death, full health, and health states worse than death (Versteegh et al., 2016). Additionally, a visual analog scale (VAS), ranging from 0 to 100, was used to quantify the health state of a patient, with 0 as the worst imaginable and 100 as the best imaginable health. The EQ5D-5L is considered a generic, valid, and reliable instrument (Feng et al., 2021).

2.3 | Costs

For the cost analysis, lip SCCs were grouped based on initial intervention. If an additional intervention was required due to inadequate resection margins, these costs were added to the initial costs. Costs were estimated from a healthcare perspective using the micro-costing method, defined as the "direct enumeration and costing of every input consumed in the treatment of a particular patient" (Hakkaart-van Roijen et al., 2015; Polsky & Glick, 2009). Preparatory activities before treatment (including imaging and consultations), overhead costs, and follow-up after treatment were not included. We calculated the costs based on registered unit codes used in our institution, which are split into costs for personnel, materials, and other costs. The costs per unit code were multiplied by the number of registered interventions in the medical records of the included patients. Admission days were calculated as the total number of admission days directly related to treating the lip SCC, including reconstruction by the plastic surgery department or extra days because of complications. As admission lengths have become considerably shorter over recent years, mean hospital admission days over the last 5 years (2015–2019) were used to provide an accurate representation of current hospital stays.

2.4 | Statistical analysis

Statistical analyses were performed using SPSS Statistics, version 25 (IBM Corp.). Descriptive statistics were used to describe baseline characteristics. Continuous data were compared using one-way ANOVAs, with post-hoc Tukey to compare more than two groups. Categorical data were analyzed using Chi-square tests, and the significance was adjusted using the Bonferroni method given the multiple testing involved. Mann–Whitney U tests were used to compare group median PROM scale scores. A univariable Cox regression was carried out to assess a priori-determined variables potentially associated with recurrence. Here, because the baseline characteristics of the brachytherapy-treated tumors were significantly different, only conventional excision and MMS treatments were compared in this way. Two-sided p-values <0.05 were considered statistically significant. The assumption of proportional hazards was checked by inspecting the Kaplan–Meier curves.

3 | RESULTS

3.1 | Patient and tumor characteristics

We identified 546 patients through PALGA and 730 patients from our own pathology department. After the removal of duplicates, the files of 642 patients were checked for eligibility. A total of 139 patients were excluded because they had a T3–T4 tumor and 50 because of nodal invasion or metastasis (Appendix A). Eventually, 336 T1–T2 lip SCCs in 324 patients were included, of which 122 (36.3%) were treated with excision, 139 (41.4%) with MMS, and 75 (22.3%) with brachytherapy. All the patient and tumor characteristics are shown in Table 1. Compared with the brachytherapy and excision group, the MMS group included significantly more females ($p<0.001$). Furthermore, patients in the MMS group were statistically older than patients receiving excision or brachytherapy treatments ($p<0.003$), more often had tumors that were located on the upper lip ($p<0.001$) or on the cutaneous part of the lip ($p<0.001$). Of the patients treated with brachytherapy, 16 (21.3%) had a previous resection of their primary tumor in another hospital, which was significantly more frequent than patients treated with excision ($n=6$, 4.9%) and MMS ($n=13$, 9.4%) ($p=<0.001$). Furthermore, the tumors in the brachytherapy group were more often T2 tumors ($n=28$, 37.3%) than tumors in the excision ($n=21$, 17.2%) and MMS groups ($n=26$, 18.7%) ($p=0.002$). Our sample included 27 immune-compromised patients, of which 15 (58%) had had a transplant. Ten of these patients were treated with MMS, four by excision, and one using brachytherapy.

3.2 | Conventional excision

Of the 122 lip SCCs that were treated with conventional excision, 48 (39%) were treated by a plastic surgeon, 48 (39%) by a Head and Neck surgeon, and 26 (21%) by a dermatologist. Seven (5.7%) had inadequate resection margins (Table 2). Three of the incompletely resected tumors were not additionally treated, two were re-excised and two patients were postoperatively treated with

TABLE 1 Patient and tumor specifications per treatment modality.

	Total ($n = 336$)	Excision ($n = 122$)	MMS ($n = 139$)	Brachytherapy ($n = 75$)	
	Mean (SD) or number (%)	Mean (SD) or number (%)	Mean (SD) or number (%)	Mean (SD) or number (%)	*p*-value
Patient characteristics					
Age, mean in years	68.4 (13.7)	67.1 (13.6)	70.8 (13.3)	66.2 (14.0)	0.025
Age, range	20–95	20–95	22–94	21–89	
Gender					
Male	224 (66.7%)	89 (73.0%)	75 (54.0%)	60 (80.0%)	<0.001*
Female	112 (33.3%)	33 (27.0%)	64 (46.0%)	15 (20.0%)	
Skin type (Fitzpatrick)					
Type I–II	283 (84.2%)	87 (71.3%)	131 (94.2%)	65 (86.7%)	
Type III–IV	13 (3.9%)	0 (0%)	7 (5.0%)	6 (8.0%)	
Type V–VI	1 (0.3%)	0 (0%)	0 (0%)	1 (1.3%)	
Unknown	39 (11.6%)	35 (28.7%)	1 (0.7%)	3 (4.0%)	
Smoking					
Current	102 (30.4%)	42 (34.4%)	31 (29.5%)	29 (38.7%)	
Former	59 (17.6%)	17 (13.9%)	29 (20.9%)	13 (17.3%)	
Never	102 (30.4%)	31 (25.4%)	41 (29.5%)	30 (40.0%)	
Unknown	73 (21.7%)	32 (26.2%)	38 (27.3%)	3 (4.0%)	
Immunodeficiency					
Yes	26 (7.7%)	10 (8.2%)	14 (10.1%)	2 (2.7%)	
No	308 (91.7%)	110 (90.2%)	125 (89.9%)	73 (97.3%)	
Missing	2 (0.6%)	2 (1.6%)	0 (0%)	0 (0%)	
Tumor characteristics					
Tumor type					
Primary tumor	264 (78.6%)	104 (85.2%)	115 (82.7%)	45 (60.0%)	
Prior excision elsewhere	35 (10.4%)	6 (4.9%)	13 (9.4%)	16 (21.3%)	
Recurrent	6 (1.8%)	1 (0.8%)	2 (1.4%)	3 (4.0%)	
Second primary tumor	18 (5.4%)	5 (4.1%)	6 (4.3%)	7 (9.3%)	
Prior excision elsewhere	3 (0.9%)	1 (0.8%)	0 (0%)	2 (2.7%)	
Recurrent	2 (0.6%)	1 (0.8%)	0 (0%)	1 (1.3%)	
Third primary	3 (0.9%)	1 (0.8%)	1 (0.7%)	1 (1.3%)	
Fourth primary	2 (0.6%)	0 (0%)	2 (1.4%)	0 (0%)	
Unknown	3 (0.9%)	3 (2.5%)	0 (0%)	0 (0%)	
Tumor differentiation					
Well	130 (38.7%)	49 (40.2%)	43 (30.9%)	38 (50.7%)	
Moderate	138 (41.1%)	44 (36.1%)	65 (46.8%)	29 (38.7%)	
Poor	29 (8.6%)	13 (10.7%)	14 (10.1%)	2 (2.7%)	
Unknown	39 (11.6%)	16 (13.1%)	17 (12.2%)	6 (8.0%)	
Tumor location					<0.001*
Lower lip	285 (84.8%)	110 (90.2%)	104 (74.8%)	71 (94.7%)	
Upper lip	51 (15.2%)	12 (9.8%)	35 (25.2%)	4 (5.3%)	
Tumor site					<0.001*
Vermillion	225 (67.0%)	78 (63.9%)	87 (62.6%)	60 (80%)	
Cutaneous	42 (12.5%)	8 (6.6%)	31 (22.3%)	3 (4.0%)	
Both	35 (10.4%)	9 (7.4%)	21 (15.1%)	5 (6.7%)	
Unknown	34 (10.1%)	27 (22.1%)	0 (0%)	7 (9.3%)	

TABLE 1 (Continued)

	Total ($n=336$)	Excision ($n=122$)	MMS ($n=139$)	Brachytherapy ($n=75$)	
	Mean (SD) or number (%)	Mean (SD) or number (%)	Mean (SD) or number (%)	Mean (SD) or number (%)	*p*-value
AJCC 7					0.001*
T1	248 (73.8%)	96 (78.7%)	109 (78.4%)	43 (57.3%)	
T2	75 (22.3%)	21 (17.2%)	26 (18.7%)	28 (37.3%)	
Unknown	13 (3.9%)	5 (4.1%)	4 (2.9%)	4 (5.3%)	
AJCC 8					0.011
T1	79 (23.5%)	26 (21.3%)	43 (30.9%)	10 (13.3%)	
T2	24 (7.1%)	4 (3.3%)	11 (7.9%)	9 (12.0%)	
T3	27 (8.0%)	13 (10.7%)	12 (8.6%)	2 (2.7%)	
Unknown	206 (61.3%)	79 (64.8%)	73 (52.5%)	54 (72.0%)	

Note: When patients had multiple interventions, they were categorized by last treatment modality. Pearson's Chi-square test for categorical data. Post-hoc ANOVA for continuous data in more than two groups.

*After Bonferroni correction tests were significant when <0.004.

external radiotherapy (PORT). Nine (7.4%) excisions had close margins (margin <2 mm), of which five were not additionally treated, two were treated with an additional lip shave, one was re-excised, and one was treated with PORT. Over the most recent 5-year period, the mean admission time for conventional excision was 0.54 days. After surgery, 17 patients (13.7%) had additional surgical interventions (reconstructions or wound closures), 11 had an additional lip shave (8.9%), and seven were given antibiotic treatment (5.6%). The most common short-term complications for patients treated using conventional excision were a wound infection or dehiscence (13.1%). Two patients were admitted to the hospital for wound dehiscence that required a repeat closure.

The mean total costs of a conventional excision were €2564.22 (Table 3). At long-term follow-up, fibrosis was the most often reported complication (8.2%). After 2 years, the local recurrence rate was 3.3% ($n=4$), and the regional recurrence rate was 5.7% ($n=7$). The median recurrence time was 5.5 months (IQR: 3.0–13.5) and the median follow-up of patients treated by excision was 102 months. Three local recurrences were successfully retreated using excision and one with brachytherapy. Two patients with a regional recurrence refused curative treatment, while the others were treated with a combination of neck dissection and PORT ($n=5$). One other regional recurrence in the neck was diagnosed 7.5 years after the initial conventional excision, which was successfully treated with neck dissection and PORT. Three patients (2.5%) treated by excision died as a consequence of either neck metastasis ($n=2$) or a combination of parotid and bone metastases ($n=1$) between 16 and 24 months after the initial lip SCC treatment.

3.3 | Mohs micrographic surgery

The characteristics of the MMS treatments of lip SCCs ($n=139$) can be found in Table 2. Three patients (2.2%) had incomplete resection margins after MMS, of which two were subsequently treated with another MMS procedure and one received PORT. Most tumors were completely excised within one round (60.3%), with a mean of 1.5 MMS rounds. On average, patients were admitted to the hospital for 1.8 days when treated using MMS. In 26 patients (18.7%), a plastic surgeon was consulted for wound closure. After MMS, 17 patients (12.1%) received antibiotic treatment and 29 (20.6%) topical oncological treatments (e.g., 5-fluoro-uracil). The most common short-term complications were wound infection and dehiscence ($n=17$, 12.2%) and hemorrhaging ($n=3$, 2.2%). One patient treated with MMS developed pneumonia, presumed due to aspiration, for which intravenous antibiotics were administered, causing a prolonged hospital stay. Two patients were re-admitted to the hospital after MMS, one due to a hemorrhage and one for a necrosectomy.

The mean costs for MMS were €3032.24 (Table 3). The median follow-up period of patients treated with MMS was 41 months. The most frequent long-term complication was the development of fibrotic scars (10.8%). The 2-year local recurrence rate was 2.2% ($n=3$), and the regional recurrence rate was 0.7% ($n=1$). Local recurrences were treated with either a second MMS ($n=1$) or brachytherapy ($n=2$). The one patient with a regional recurrence was not treated curatively as a PET-CT revealed a potentially malignant mass in the pancreas and multiple lung lesions and died 21 months after the initial treatment of the lip SCC.

3.4 | Brachytherapy

Seventy-five lip SCCs were treated with brachytherapy, with a median radiation dose of 44 Gy given in 14 fractions (Table 2). Patients undergoing brachytherapy were admitted to the hospital for an average of 9.7 days. Six of these patients received antibiotic treatment (8.0%) and five topical oncological treatments (6.7%). The most often reported short-term complication was severe mucositis

TABLE 2 Treatment characteristics and medical outcomes.

	Total ($n=336$)	Excision ($n=122$)	MMS ($n=139$)	Brachytherapy ($n=75$)
	Mean (SD) or number (%)	Mean (SD) or number (%)	Mean (SD) or number (%)	Mean (SD) or number (%)
Treatment characteristics				
Dual therapy in EMC		7 (5.7%)	3 (2.2%)	3 (4.0%)
Prior excision in EMC		7 (5.7%)	1 (0.7%)	2 (2.7%)
Prior MMS in EMC		0 (0%)	2 (1.4%)	1 (1.3%)
Inadequate resection margin		7 (5.7%)	3 (2.2%)	-
Narrow resection margins		9 (7.4%)	-	-
Mohs rounds		-	1.54 (0.8)	-
1		-	85 (60.3%)	-
2		-	44 (31.2%)	-
3		-	7 (5.0%)	-
4		-	4 (2.8%)	-
5		-	1 (0.7%)	-
Radiation dose, Gy		-	-	44 (44–44)
Fractions		-	-	14 (14–14)
Reconstruction plastic surgeon		5 (4.1%)	26 (18.7%)	-
Average admission (days - last 5 years)		0.54	1.77	9.71
Medical outcomes				
Short-term complications				
Wound problem	37 (11.0%)	16 (13.1%)	17 (12.2%)	4 (5.3%)
Necrosis	4 (1.2%)	1 (0.8%)	3 (2.2%)	-
Secondary hemorrhage	3 (0.8%)		3 (2.2%)	-
Severe mucositis	35 (10.4%)	-	-	35 (46.7%)
Complications requiring hospital admission	5 (1.5%)	2 (1.6%)	3 (2.2%)	-
Long-term complications				
Radiation ulcer	10 (3.0%)			10 (13.3%)
Fibrosis	31 (9.3%)	10 (8.2%)	15 (10.8%)	6 (8.0%)
Dysesthesia	15 (4.5%)	3 (2.5%)	6 (4.3%)	6 (8.0%)
Atrophy	8 (2.4%)	1 (0.8%)	1 (0.7%)	6 (8.0%)
Recurrence	25 (7.4%)	12 (9.8%)	4 (2.9%)	9 (12.0%)
Local recurrence	9 (2.7%)	4 (3.3%)	3 (2.2%)	2 (2.7%)
Regional recurrence	16 (4.8%)	8 (6.6%)	1 (0.7%)	7 (9.3%)
Distant metastases	3 (0.9%)	1 (0.8%)	0 (0.0%)	2 (2.7%)
Secondary primary tumor	18 (5.4%)	10 (8.2%)	3 (2.2%)	5 (6.7%)
Death due to tumor	6 (1.8%)	3 (2.5%)	1 (0.7%)	2 (2.7%)

Note: For treatment characteristics and medical outcomes, patients were grouped based on the last performed treatment.

($n=35$, 46.7%). The mean costs of brachytherapy for lip SCC were €13,311.24. The median follow-up period after brachytherapy was 76 months. The most prevalent long-term complications following brachytherapy were radiation ulcers (13.3%), fibrosis (8.0%), and atrophy (8.0%). The 2-year follow-up rate was 2.7% ($n=2$) for local recurrences and 6.7% ($n=5$) for regional recurrences. A further two regional cervical recurrences (2.7%) were found 29 and 35 months after initial treatment. The local recurrences were treated successfully with excision and MMS. Two regional recurrences were successfully treated with neck dissection and another two with neck dissection and PORT. Two patients (2.7%) who were treated with neck dissection and PORT died due to lymphangitis carcinomatosa and malignant pleural effusion, respectively, 15 and 47 months after initial treatment.

3.5 | Locoregional recurrences

Overall, 25 out of 336 tumors recurred (7.4%), of which nine were local recurrences and 16 regional recurrences. All the local

TABLE 3 Costs of conventional excision, Mohs micrographic surgery, and brachytherapy.

Costs	Excision ($n=126$) Euro	MMS ($n=139$) Euro	Brachytherapy ($n=71$) Euro
Personnel	897.30	1078.11	4983.80
Material	296.10	364.40	1081.70
Pathology	331.82	511.00	-
Reconstruction plastic surgery	233.99	218.17	-
Medication/additional treatment	140.20	100.52	31.21
Admission days	222.77	626.79	7214.53
Subtotal	€2122.18	€2898.99	€13,311.24
Additional treatment			
Additional excision	216.20	-	-
Additional MMS	22.58	40.99	-
Additional brachytherapy	203.26	92.26	-
Total	€2564.22	€3032.24	€13,311.24

Note: Costs were estimated from a healthcare perspective with the micro-costing method. Only costs directly related to the specific therapy are included. Work prior to treatment (such as imaging and consultations), overhead costs, and follow-up after treatment are not included in this comparison.

TABLE 4 Tumor recurrence of lip SCCs treated in our institute.

	Recurrences ($n=25$) Mean (SD) frequency (%)
Local recurrence	9 (36.0%)
Regional recurrence	16 (64.0%)
Recurrence time, months	14.3 (18.3)
Treated in EMC	25 (100%)
Treatment type	
Excision	2 (8.0%)
Excision + neck dissection	1 (4.0%)
MMS	2 (8.0%)
Brachytherapy	3 (12.0%)
Shave excision	1 (4.0%)
Neck dissection	2 (8.0%)
Neck dissection + PORT	11 (44.0%)
Palliative RT	1 (4.0%)
Best supportive care	2 (8.0%)
Death due to tumor	6 (24.0%)
Follow-up time, months	64.2 (48.7)

recurrences were successfully treated with excision, MMS, or brachytherapy. Regional recurrences were treated with either a neck dissection (ND) or a combination of ND and PORT. Eventually, 6 out of the 16 patients with regional recurrences (37.5%) died due to their tumor. Table 4 provides an overview of the recurrence characteristics. A univariable Cox analysis showed that the T stage (T2: HR 3.5; CI 1.6–7.7) and poor tumor differentiation (compared to good and moderate differentiation, HR 5.6; CI 2.4–13.1) were associated with a higher risk of locoregional recurrence. Sex, tumor location, immune status, previous recurrences, and the number of previous lip tumors were not associated with the risk of a locoregional recurrence. A univariable Cox regression showed that MMS had a significantly lower likelihood of recurrence than treatment using conventional excision (MMS: HR 0.646; CI 0.05–0.65).

3.6 | Patient-reported outcomes

We sent PROMs to 177 patients who were still alive at the start of this study and 82 patients (46.3%) returned fully complete responses. Of these, 19 were from patients treated with excision (23.2%), 46 had been treated with MMS (56.1%), and 17 with brachytherapy (20.7%). An overview of the outcomes can be found in Table 5. Patients generally reported a good QoL. The median FACE-Q H&N scores were high in all the subdomains. The median "oral competence" score was the lowest of the function scales (median: 87.0, IQR: 66–100). Furthermore, the "cancer worrying" subdomain had the lowest score of the health-related QoL domains (median: 81, IQR: 71–81). Patients treated for a T2 tumor reported more problems with facial appearance (median 81, IQR 66–100) than patients with a T1 tumor (median 100, IQR: 100–100, $p=0.001$). Further, their median score on oral competence was also lower (T1: 100, IQR 66–100, T2: 75, IQR 66–100), although this was not a significant difference ($p=0.160$). Patients receiving more than one intervention (due to a previous inadequate resection in another institution, or a re-intervention due to inadequate margins or a recurrence) reported significantly more problems with smiling (median 88, IQR 68–100) than patients with a single intervention (median: 100, IQR 88–100, $p=0.015$). Out of the 29 patients who wore dentures, 10 (34%) experienced problems

TABLE 5 Patient-reported outcomes for the total group of patients.

		Patients ($n = 82$)
	Range	Median (IQR)
EQ-5D-5L	−0.446 to 1	1.0 (0.85–1.0)
Health on VAS	0–100	80 (73–90)
Face-Q, appearance scale		
Appearance of face overall	0–100	100 (89–100)
Face-Q, function scale		
Eating and drinking	0–100	100 (87–100)
Oral competence	0–100	87.0 (66–100)
Smiling	0–100	100 (88–100)
Speaking	0–100	100 (100–100)
Face-Q, health-related QoL		
Appearance/face distress	0–100	100 (77–100)
Drooling distress	0–100	100 (100–100)
Eating distress	0–100	100 (100–100)
Smiling distress	0–100	100 (100–100)
Speaking distress	0–100	100 (100–100)
Cancer worry	0–100	81 (71–81)

with the fit following treatment, necessitating subsequent adjustment or replacement of the denture.

4 | DISCUSSION

As far as we are aware, with 336 treated lip SCCs, this is the largest single-center retrospective cohort study in which medical outcomes, patient-reported outcomes, and costs of conventional excision, Mohs micrographic surgery (MMS), and brachytherapy treatments for T1–T2 N0M0 lip SCCs are reported. To date, no consensus has been reached about the preferred treatment modality for this type of cancer (Campbell, 1998; Conill et al., 2007; Han et al., 2016). Due to the few locoregional recurrences and tumor-related deaths, it was not possible to compare treatment outcomes after adjusting for differences in baseline characteristics such as T stage or tumor differentiation. Patients treated using brachytherapy were relatively more often classed as having a T2 tumor (37% of those treated in this way), whereas this was only the case in 17% of excisions and 18% of MMS procedures. Comparing MMS with conventional excision treatments, we found that MMS had a significantly lower recurrence rate. Disease-specific survival (DSS) in our overall cohort was high (98.2%) but decreased significantly if a patient developed a regional recurrence (DSS = 62.5% after a median follow-up of 30 months).

In total, nine local recurrences (2.7%) and 16 regional recurrences (4.8%) were detected in our sample. Other studies evaluating excision, MMS, or brachytherapy found similar levels of local recurrences (range: 1%–9%) and regional recurrences (4%–8%) in early stage lip SCCs (Guibert et al., 2011; Howard et al., 2021; Kristensen et al., 2017; Ozkul et al., 2016; Wang et al., 2018). In our study, all the recurrences were diagnosed within 3 years of initial treatment, apart from one regional recurrence which occurred 7.5 years after treatment. This is in line with the existing literature that reports that 95% of recurrences occur within 3 years of treatment (Bilkay et al., 2003; Kristensen et al., 2017). We saw that patients with a T2 lip SCC or poor tumor differentiation had a higher risk of locoregional recurrences. This is again in line with earlier research, which similarly found that T2 lip SCCs or poor tumor differentiation increased the risk of developing recurrences and metastases (Ant et al., 2019; Brinkman et al., 2015; Tokez, Venables, et al., 2022). Since, in our study, patients treated with brachytherapy more often had a T2 tumor, it was not possible to compare the likelihood of a recurrence with the other treatment modalities. However, we did find that MMS resulted in a significantly reduced likelihood of recurrence than conventional excision. Still, we were not able to correct for confounders.

The disease-specific survival rate in patients treated for regional recurrences was lower than the 79.1% disease-specific 5-year survival for patients with metastatic cutaneous SCCs in any location based on overall population SCC survival data (Tokez, Wakkee, et al., 2022). This suggests that, once they become metastastatic, lip SCCs have a worse prognosis.

Both generic (EQ5D-5L and VAS) and disease-specific QoL (FACE-Q) were rated highly, indicating that the treatment for T1–T2 lip SCCs generally has a low impact on QoL and functional and cosmetic outcomes at long-term follow-up. These findings are comparable to another study on the long-term QoL of a cohort of 105 patients treated for a lip SCC (Schüller et al., 2015). As our questionnaires were only administered once, at the long-term follow-up point, we do not know whether the baseline patient-reported outcomes were similar among the treatment groups and, therefore, it is impossible to state that one of the treatment modalities had a better long-term QoL than the others.

Patients treated for a T2 tumor did have more problems with facial appearance. Schüller et al. (2015) similarly found that patients with a T2–T3 tumor had more problems with lip pursing. Additionally, patients in our cohort treated with multiple interventions reported significantly more problems with smiling than patients treated only once, which is also in line with other studies (Gulati et al., 2022; Zebolsky et al., 2021). This suggests that a previous inadequate resection negatively influences QoL at the long-term follow-up stage, emphasizing the need for initial treatment in a specialized center, where all the treatment modalities are available. This would make it possible to incorporate patient preferences, patient-reported outcomes, and risk factors for complications in decision-making during multidisciplinary consultations. Finally, 34% of the patients with dentures had problems with the fit after treatment. This should be acknowledged when informing patients about their expected outcomes after treatment. As such, we would recommend that such patients be seen by a maxillofacial surgeon before treatment.

Because a baseline comparison of the groups was not possible, a direct comparison of the costs of the treatment modalities was not possible. However, an aim was to create awareness among healthcare experts by providing an overview of the mean

calculated costs for each treatment modality. We estimated the Brachytherapy treatment as costing €13,311, which is approximately €10,000 more expensive than both excision and MMS. This difference in costs is primarily explained by the lengthy duration of the intervention, resulting in more personnel costs and admission overheads. On this basis, we think that MMS would be the most logical treatment option for most non-complex early-stage lip SCCs. Nevertheless, for certain patients with a T1–T2 lip SCC, brachytherapy may still be the preferred treatment (i.e., where there is a difficult tumor location, recurrent tumor, or previous interventions). We would suggest that decisions regarding treatment in these specific cases should be made by a multidisciplinary team of head and neck surgeons, dermatologists, plastic surgeons, and radiotherapists, in which a patient's preferences, frailty, and risk factors for complications are taken into account. When looking at the interventions for early stage lip SCC during the past 24 years at our institute, we already see a shift in treatment options applied (Appendix B). From 1996 to 2007, most lip SCCs were treated using conventional excision, while, in the last 5 years, 76.7% of lip SCCs have been treated with MMS, 13.2% with brachytherapy, and only 10.1% by excision.

4.1 | Strengths and limitations

As our institute is a specialized center, we have treated sufficient patients to be able to report on the outcomes of the three most frequent treatment modalities. Furthermore, we are the first to report on the medical outcomes, patient-reported outcomes, and costs to provide a comprehensive overview of different aspects of the available treatment modalities. Further, the long-term follow-up consequences have been described, and potential inabilities to follow up some recurrences were reduced by linking to the national pathology database.

The retrospective design of this study imposes limitations. As a consequence, some data are missing, especially related to the older cases. Data on depth of invasion, perineural invasion, and vaso-invasive growth were missing in almost 60% of the pathology reports, and so we were not able to use the AJCC8 classification in our analyses. Nevertheless, we believe that it is justified to base our reporting on the earlier AJCC7 classification since the majority of our cohort was treated before the AJCC8 classification was introduced. Further, there is the possibility of an indication-based bias since the brachytherapy group contained a higher percentage of T2 tumors. Another limitation of the retrospective study design was that we were only able to calculate mean costs using the micro-costing method from a healthcare perspective. As such, costs incurred in working up to and following the treatment, and indirect costs, were not taken into account. Nowadays, time-driven activity-based costing (TDABC) is seen as the preferred method for cost calculation. In TDABC, costs are assessed according to the time a treatment takes as well as the accuracy and outcomes of the treatment. However, such an approach is only possible in a prospective study.

Finally, the questionnaires were only completed at long-term follow-up which meant it was not possible to report on cost-effectiveness. Almost half of the included patients had died by the time of analysis, which was not unexpected since lip SCCs often appear at a late age and some of the included patients were treated more than 20 years ago. As a consequence, patient-reported outcomes were only available for 82 patients, and most of these had undergone MMS in recent years.

4.2 | Clinical implications

As the treatment of lip SCCs is not suitable for a randomized controlled trial, observational cohort studies offer the best evidence we can have. Both disease-specific survival and patient-reported QoL were high for all the treatment modalities, and therefore, costs should be an important factor in the decision-making process. Brachytherapy was three times more expensive than the alternatives and should therefore only be considered when there are specific indications (such as T2 SCCs or for patients with prior treatment that can affect facial appearance). Based on the lower risk of a locoregional recurrence with MMS than with excision, and their similar costs, we would see MMS as the preferred treatment for low-risk T1 lip SSCs, especially since regional recurrences significantly affect disease-specific survival. Our results could be used to inform patients and their caregivers about the long-term outcomes of the three alternative treatment modalities. Following prospective cohorts, in which patient-reported outcomes are collected by default at baseline and during the follow-up course, would be a sensible next step in evaluating the impact of the treatment modalities on oral functioning, QoL, and cosmetic outcomes during short- and long-term follow-up assessments. In the future, we believe it would be helpful if information on medical outcomes, QoL, facial appearance, and facial function could be provided in a decision aid for patients and healthcare professionals who have to make decisions about the treatment of a lip SCC.

5 | CONCLUSIONS

Generally, a squamous cell carcinoma of the lip has a good prognosis, with a disease-specific survival rate of 98.2%, a high QoL, and patient satisfaction with good functional and cosmetic outcomes at long-term follow-up. When taking costs and the risk of locoregional recurrences into account, our study suggests that, for most non-complex T1 lip SCCs, Mohs micrographic surgery would be the most logical treatment. However, for some patients (e.g., those at T2), brachytherapy or conventional excision could still be a preferable treatment option.

AUTHOR CONTRIBUTIONS

Kira S. van Hof: Investigation; writing – original draft; methodology; validation; visualization; data curation; formal analysis; software;

conceptualization. **Marlies Wakkee:** Conceptualization; methodology; validation; writing – review and editing; supervision; investigation; data curation. **Aniel Sewnaik:** Writing – review and editing; validation; methodology; conceptualization; supervision; investigation; data curation. **Aimée F. Herkendaal:** Formal analysis; validation; methodology; software; investigation; data curation; visualization; writing – original draft. **Lisa Tans:** Writing – review and editing. **Hetty Mast:** Writing – review and editing. **Renate R. van den Bos:** Writing – review and editing. **Marc A. M. Mureau:** Writing – review and editing. **Marinella P. J. Offerman:** Writing – review and editing; methodology; supervision; conceptualization. **Robert J. Baatenburg de Jong:** Conceptualization; writing – review and editing; supervision.

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None.

CONFLICT OF INTEREST STATEMENT

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Although the data are not yet available in a public database, the authors are willing to share data upon request.

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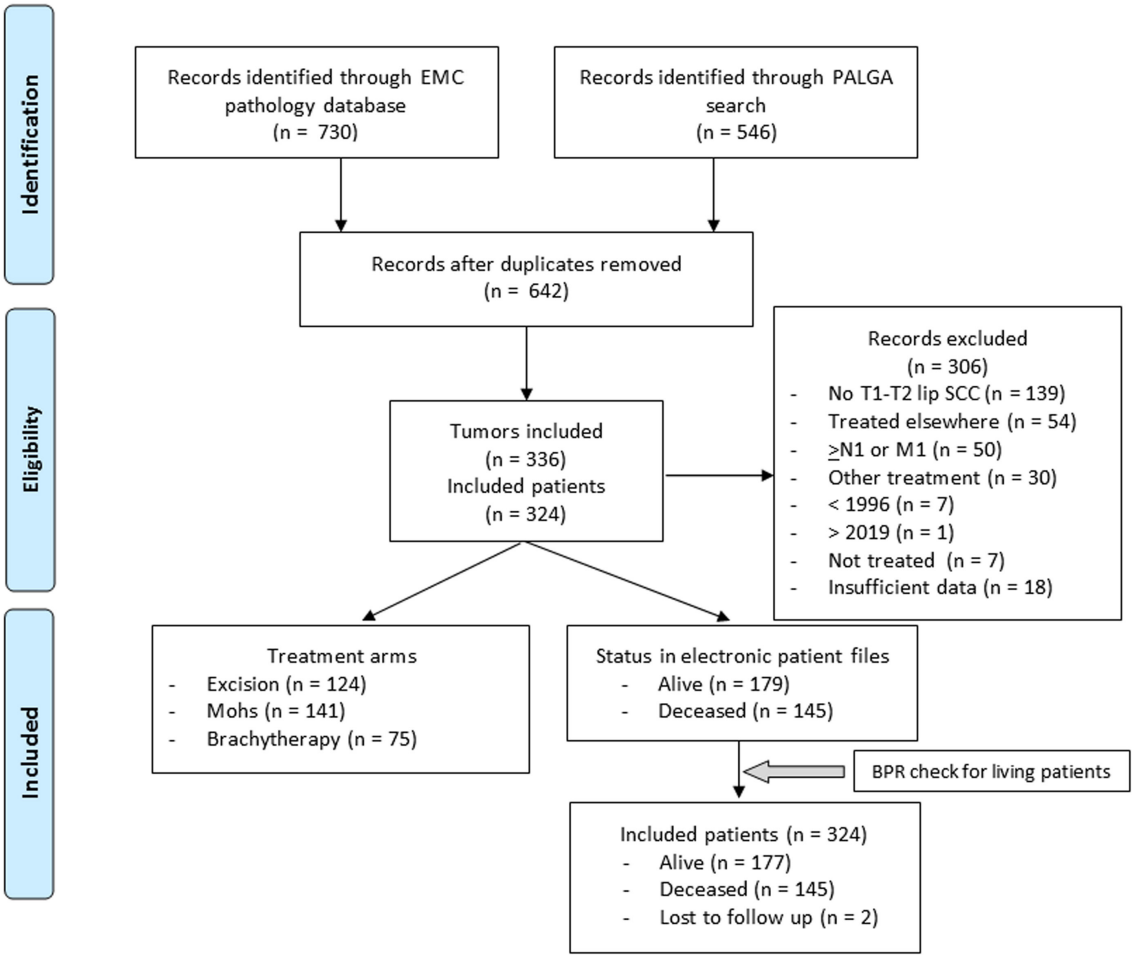
APPENDIX A



APPENDIX B