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Factors affecting the recurrence of early-stage lip cancer

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ABSTRACT

***Background*:** To determine the patterns of recurrence, prognostic factors and treatment outcomes in stage I-II lip cancer. ***Materials and Methods*:** A retrospective review was made of the data of 74 patients diagnosed with squamous cell carcinoma (SCC) of the lip between 2000 and 2009. ***Results*:** In all, 44 of the patients had stage I disease and 30 had stage II disease. Surgery was performed on the primary tumor in all patients, 15 received adjuvant radiotherapy and 23 underwent elective neck therapy. Recurrence occurred in 23 (31%) of the patients, with a mean time from surgery to relapse of 23 months. The frequency of nodal recurrence increased as tumor stage and depth increased. Adjuvant radiotherapy and neck dissection or elective radiotherapy decreased the risk of recurrence in tumors with depths of over 0.5 cm, with positive or close margins, and with perineural invasion. The median overall survival (OS) was 120 months and the median disease-free survival (DFS) was 83 months. A univariate analysis revealed tumor stage and depth, adjuvant radiotherapy, and neck treatment (lymphatic dissection + nodal irradiation) to affect DFS, while a multivariate analysis showed that elective neck radiotherapy improved DFS. ***Conclusion*:** Greater tumor stage and depth increase the risk of nodal recurrence in early-stage lip cancer, although the frequency of recurrence is decreased in such patients if treated with elective neck dissection and/or postoperative radiotherapy.

INTRODUCTION

Lip cancer usually has a good prognosis, which may be attributed to the early diagnosis associated with the location of the tumor. Tumors of the lip require special consideration as their natural history differs from oral cavity disease [1]. In general, local control shows a survival rate, greater than 5 years, and a mortality rate of 10–15%, representing a better prognosis than other head and neck tumors [2]. The most important factors related to prognosis are lymph node metastasis and tumor size [3,4], although patients with tumors smaller than 4 cm and no lymph node metastasis or regional invasion – those in whom a good prognosis is anticipated – recurrence does occur. Recurrence treatments are less successful than primary treatments [5], with an estimated success rate of approximately 60% [6,7]. While the survival rate in local recurrence is reported to be 78%, patients with regional recurrence have a survival rate of 52% [8]. As such, preventing recurrence is an important aspect of primary treatment efforts.

Studies investigating the prognostic factors affecting early-stage lip cancer are few in number. The present study aims to elucidate the selection of patient candidates for more aggressive treatment by revealing the recurrence patterns in early-stage lip cancer with a long follow-up period of 10 years.

MATERIALS AND METHODS

In the present study, a retrospective review was made of the data of 74 patients diagnosed with stage I -II SCC of the lip who were treated at the Radiation Oncology Clinic of Kartal Research and Education Hospital between 2000 and 2009. All patients were treated using a Varian Clinac DHX (Varian Medical systems, California, USA) device. The Varian Clinac DHX High Performance linear accelerator makes use of 6 MV and 18 MV X-ray energies, and has six different electron energies – 4, 6, 9, 12, 15 and 15 MeV – for use in electron therapies. The dose rate of all energy can up to 600MU/min. Linac has 80 multi leaf collimator (MLC) and can be used on any geometry without the need for protection blocks. The leaves move independently of each other.

The patient data collected included age at presentation, gender, classification of malignant tumors (TNM), pathological details, treatment details, recurrence pattern and outcome. Early-stage disease (stage I and II) was defined as tumors <4 cm without deep invasion into the surrounding structures and no evidence of lymph node involvement [9]. The

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pathological analyses included evaluations of tumor location (upper/inferior lip, with/without invasion of the commissure), tumor size, tumor depth, differentiation, perineural invasion, mucosal invasion and surgical margin. The patients were grouped according to treatment modality: with and without neck dissection, and with and without post-excision radiotherapy. Local failure was defined as disease recurrence at, or close to, the primary site, while regional failure was defined as the recurrence of disease in the draining regional lymph nodes. To analyze DFS, the recurrence of disease at the primary, regional or distant site was considered an event. All estimates were calculated from the date of surgery to the defined event (if any), the last patient contact, or death.

Differences in the recurrence rates were compared with a Chi-square test, the local control rate, DFS and OS were determined using the Kaplan-Meier method, and prognostic factors were compared with a log-rank test. A multivariate analysis was conducted using the Cox proportional hazard model. p values <0.05 were considered statistically significant.

The institutional board of the Eskişehir Osmangazi University Faculty of Medicine gave approval for the study (dated 18.02.2020, and numbered 25403353-050.99-E.27534), which was carried out in accordance with the principles set out in the Declaration of Helsinki and all applicable regulations.

RESULTS

In total, 74 patients with early-stage SCC of the lip were evaluated. The median age at presentation was 59.6±12.8 years (range: 31–91 years); 59 (80%) of the patients were male and 15 (20%) were female. The tumor location was the lower lip in 61 (82%) of the patients and the upper lip in 13 (18%). Of the total sample, 44 of the patients (59%) had stage I disease and 30 (41%) had stage II disease. Patient characteristics and clinicopathological details are presented in (table 1).

The primary tumor of all patients was treated surgically, while 15 (20%) patients with mucosal and commissure invasion and perineural invasion received adjuvant radiotherapy (200–250 cGy/fr, and a median of 50 Gy [range: 20–66 Gy]). In total, 19 (26%) of the patients underwent a neck dissection and four (5%) received elective neck radiotherapy (200 cGy/fr and a median of 46 Gy [range: 20–50 Gy]). Recurrence was observed in 23 (31%) patients, of which 24% were regional, 4% were local, and 3% were regional + local (table 2). The median time to recurrence was 23 months (range: 1.5–62 months). Among the 59 patients treated only with surgery, 22 (37%) experienced recurrence, whereas only 1 of the 15 (7%) patients that received adjuvant radiotherapy experienced recurrence. Among the patients that received neck treatment (dissection: n=19; elective radiotherapy: n=4), only two (9%) experienced regional recurrence, whereas among the 51 patients that did not receive neck treatment, 21 (41%) experienced recurrence (local: n=3; regional: n = 16; local + regional: n=2). Among the 23 patients who experienced recurrence, the frequency of nodal recurrence increased as the tumor stage and depth increased (p=0.01) (table 3). Adjuvant radiotherapy and lymphatic dissection or elective radiotherapy of the neck decreased the risk of recurrence in this group of patients (p=0.01 and p=0.02, respectively) (table 4).

Table 1. Tumor and treatment characteristics for all patients.

		n	%
Sex	Male	59	80
	Female	15	20
Age	≤60	35	47
	>60	39	53
T Stage	I	44	60
	II	30	40
Localization	Upper lip	13	18
	Lower lip	61	82
Infiltration of the mucosa	Yes	4	5
	No	70	95
Commissure invasion	Yes	5	7
	No	69	93
Surgical margins	Microscopically positive	5	7
	<0.5 cm	27	36
	0.5–1 cm	37	50
	>1cm	5	7
Depth of tumor	<0.5 cm	22	30
	0.5–1 cm	52	70
Perineural invasion	Yes	16	22
	No	58	78
Grade	I	35	47
	II	35	47
	III	4	6
Treatment	Only surgery	59	80
	Surgery + postoperative radiotherapy	15	20
Neck treatment	No	51	69
	Neck dissection	19	26
	Elective neck radiotherapy	4	5

Following salvage therapy (surgery + postoperative radiotherapy), the disease was fully controlled in 14 (65%) patients, whereas complete control was not achieved in nine patients following salvage therapy. In total, 64 of the patients (87%) were disease-free within a mean follow-up period of 42 months (range: 2–128 months). In all, nine (12%) patients died from the disease, whereas one (1%) patient died from unrelated causes. The median OS was 120 months (95% CI: 77–164), and the 3- and 5-year OS were 90% and 80%, respectively. The median DFS was 83 months (95% CI: 62–105); the median 3-year DFS was 68% and the median 5-year DFS was 65%. The effects of gender, age, disease stage, lower and upper lip localization, mucosal

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invasion, commissural invasion, surgical margin, tumor depth, perineural invasion, tumor differentiation, adjuvant radiotherapy and neck therapies were investigated with a univariate analysis (table 5), revealing the stage and depth of the tumor, adjuvant radiotherapy, and neck therapy to affect DFS. A multivariate analysis, on the other hand, revealed elective neck treatment to improve DFS (table 6).

Table 2. Site of recurrence for treatment group.

	Surgery (n = 59)	Surgery + radiotherapy (n = 14)	Local radiotherapy (n = 51)	Local and neck radiotherapy (n = 23)
Lip	3	-	3	-
Lymph node	17	1	16	2
Lip + lymph node	2	-	2	-
Total	22 (37% within surgery group)	1 (7% within radiotherapy group)	21 (41% within local therapy group)	2 (9.5% within local and neck therapy group)

Table 3. Recurrent patient characteristics.

	Patient characteristics (n)	Recurrence		p
		n	%	
Sex	**Male (59)**	18	30	NS*
	Female (15)	5	33	
Age	**≤60 (35)**	11	31	NS
	>60 (39)	12	31	
T Stage	**I (44)**	9	21	**0.01**
	II (30)	14	47	
Location	**Upper lip (13)**	5	39	NS
	Lower lip (61)	18	30	
Infiltration of the mucosa	**Yes (4)**	1	25	NS
	No (70)	22	31	
Commissure invasion	**Yes (5)**	-	-	NS
	No (69)	22	31	
Surgical margins	**Microscopically positive (5)**	2	40	NS
	≤0.5 cm (27)	6	22	
	0.6–1 cm (37)	14	38	
	≥1 cm (5)	1	20	
Depth of tumor	**≤0.5 cm (22)**	2	9	**0.01**
	0.6–1 cm (52)	21	40	
Perineural invasion	**Yes (16)**	4	25	NS
	No (58)	19	32	
Grade	**I (35)**	11	31	NS
	II (35)	11	31	
	III (4)	1	25	

Table 4. Treatment characteristics of recurrent patients.

	Patient and tumor characteristics (n)	Recurrence		p
		n	%	
Surgical margins	**Microscopically positive (5)**	2	40	NS*
	≤0.5 cm (27)	6	22	
	0.5–1 cm (37)	14	38	
	>1 cm (5)	1	20	
Neck treatment	**No (51)**	21	41	**0.01**
	Neck dissection (19)	2	10	
	Elective neck radiotherapy (4)	-	-	
Treatment	**Only surgery (59)**	22	37	**0.00**
	Surgery + postoperative radiotherapy (15)	1	17	

Table 5. Disease-free survival.

		3 years disease-free survival (%)	p*
Sex	**Male**	68	NS*
	Female	66	
Age	**≤60**	70	NS
	>60	66	
T Stage	**I**	83	**0.03**
	II	48	
Location	**Upper lip**	52	NS
	Lower lip	72	
Infiltration of the mucosa	**Yes**	70	NS
	No	86	
Commissure invasion	**Yes**	69	NS
	No	72	
Surgical margins	**Microscopically positive**	40	NS
	≤0.5 cm	77	
	0.5–1 cm	64	
	>1 cm	80	
Depth of tumor	**≤0.5 cm**	89	**0.03**
	0.5–1 cm	53	
Perineural invasion	**Yes**	79	NS
	No	68	
Grade	**I**	55	NS
	II	78	
	III	66	
Treatment	**Only surgery**	65	**0.04**
	Surgery + postoperative radiotherapy	80	
Neck treatment	**Yes**	90	**0.01**
	No	60	

*NS: Not significant

Table 6. Multivariate analysis for disease-free survival

	Sig.	Exp (B)	% 95 CI
Stage	NS*	1.66	0.71–3.88
Depth of tumor (0.5 cm)	NS	4.5	0.00–4.09
Postoperative radiotherapy	NS	0.35	0.04–2.61
Elective neck treatment	**0.03**	0.22	0.05–0.92

p <0.05 Cox multivariate test, *NS: Not significant

DISCUSSION

In general, the prognosis of early-stage SCC of the lip is very good, with 10-year DFS rates of 94% and 78% for stage I and II disease, respectively [10]. Nonetheless, in this patient group – in which the probability of cure is high – recurrences and disease-related mortalities do occur. Lip cancer case series have reported recurrence rates of 7–30% of patients [10,11], and local recurrence in 3–12%, whereas nodal recurrence occurs in 4–20% of patients [10,11]. In the present study, the local recurrence rate was 7%, which concurs with previous reports, although the isolated nodal recurrence rate in the present study (24%) was much higher than in previous studies. A correlation has been identified between tumor size and nodal metastasis [12]. The high nodal recurrence rate observed in the present study may be attributable to the fact that 41% of the tumors were T2 and 81% were >0.5 cm in depth.

The optimum management of the N0 neck in early

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-stage lip cancer patients remains controversial. Retrospective studies suggest that subclinical disease in patients with early-stage head and neck carcinoma can be successfully eradicated with radiotherapy or neck dissection [6]. Elective lymph node dissections can provide information about the disease stage, and can indicate a need for adjuvant therapy, while also being reported to decrease the risk of locoregional recurrence and metastasis [5,13]. Kligerman *et al*. reported a better DFS (3- and 5-year rates of 72% and 49%, respectively) and better nodal recurrence rates (42% and 24%, respectively) in patients with T1 and T2 oral cavity tumors that were treated with resection and supraomohyoid neck dissection, when compared to those that only underwent a resection [5]. In patients in whom dissection was not performed elective neck, radiotherapy is a good alternative. In the present study, among the patients who underwent nodal elective therapy, the nodal recurrence rate was lower (9.5% vs. 35%) and the 3-year DFS rate was higher (90% vs. 60%) than in those that did not, and four of the patients who underwent elective nodal therapy received radiotherapy as the elective neck treatment.

In the present study, the recurrence rate in the patients that underwent postoperative radiotherapy was lower than those treated only surgically (7% and 37%, respectively). Veness *et al*. reported a high (19%) nodal recurrence rate, similar to the present study [11], and reported the nodal recurrence rate to be higher in patients treated only with surgery than in those treated with radiotherapy.Kerawala *et al.* made a retrospective comparison of surgery and radiotherapy, and reported a higher nodal recurrence rate in the radiotherapy group, which they attributed to that fact that the tumor sizes in this group were larger [1]. Zitsch *et al.* observed the incidence of both regional and local recurrence to be significantly lower than expected in patients treated initially with surgery, and significantly higher than expected in those treated initially with radiation or combination therapy [14]. The fact that these studies are all retrospective, as with the present study, and the fact that therapy modalities were chosen according to patient characteristics, make the findings hard to interpret. In the present study, however, the addition of postoperative radiotherapy in patients with such negative prognostic factors as lymphovascular invasion or perineural invasion improved the outcomes.

No correlation was observed between recurrence and age, gender, lip sub-site, perineural invasion, histologic grade or surgical margin status in the present study. Baisya *et al.* reported tumor size alone to be a significant independent prognostic factor of recurrence [15]. A India study reported a 40.0% recurrence rate for T3-4 cancers, but only a 24.5% recurrence rate for T1-2 cancers [15]. Similarly, MacComb *et al.* reported recurrence to be related to tumor stage and differentiation (a 3% local recurrence rate for tumors <2 cm versus 21% for tumors >2 cm) [10]. Walton *et al*. observed a difference in lymph node metastasis in patients with T1 tumors and those with T2 tumors [16]. An increase in delayed metastasis was observed in patients with tumors >3 cm.

Other clinical and histologic factors have been investigated in the present study in an attempt to determine which patients are at the highest risk of developing regional lymph node disease. Tumor thickness may be a useful parameter for the prediction of occult metastasis in SCC of the lip. There have been numerous studies analyzing the effect of tumor thickness on prognosis in carcinomas of the oral cavity, but to date, this "third dimension" has not been used as routine in treatment planning [17,18]. Pantenero *et al.* reported that the lack of standard sampling and measurement techniques and cutoff values makes it nearly impossible to compare the findings reported in literature, although most studies report a tumor thickness >2–5 mm to be associated with the presence of occult metastases, and reduced DFS and OS [18,19]. There have been several studies identifying invasion depth as a risk factor for lymph node metastasis in lip SCC and oral cavity cancer [20,21], although Walton *et al.* reported, in their subset analysis of patients with available depth information, found that this had no significant impact on the determination of lymph node metastasis [16]. In the present study, no nodal recurrence was observed in any of the patients with tumors ≤5 mm, whereas patients with tumors ≥6 mm all experienced a nodal relapse, and the difference was statistically significant.

Patients with locally recurrent lip cancer recorded a significantly higher rate of cervical lymph node metastasis than those without local recurrence (15% versus 2%) [14]. In patients with local recurrence, elective neck treatment was recommended due to the high rate of nodal involvement [21], while in the present study, local and nodal metastasis – together, and following each other – was observed in two patients, and therefore their results were not commented on.

Perineural invasion occurs via contiguous spread, along with the potential space that exists inside the nerve sheath surrounding a nerve. Accordingly, perineural spread in head-and-neck cancers is infrequent, but can lead to the aggressive manifestation of the disease where present [22,23]. Previous studies have addressed the role of perineural invasion in the development of lymph node metastases [16]. A univariate analysis showed perineural invasion to be significantly associated with lymphatic node recurrence [24]. Another study reported no significant difference in the local control and OS rates of patients with and without perineural invasion [23]. In a study involving 109 upper lip-cancer patients, regional recurrence was seen in 13.8% of the sample, while in a multivariate analysis, the

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invasion depth (p=0.003) and degree of differentiation (p=0.023) were associated with regional recurrence [24]. In another study, involving 144 lip-cancer patients, 84% were stage I-II, and clinical staging was related to a specific higher survival rate (p= 0.0049). Among 112 cases (77.78%) who underwent surgical treatment, only six patients (4.80%) experienced local recurrence, all of which were directly associated with compromised surgical margins (p=0.0320) [3].

There are new articles reporting an increase in tumor depth and nodal recurrence of the stage, and so there is need for future prospective randomized researches because of new articles of the elective neck treatment and post-operative radiotherapy researches.

CONCLUSION

Tumor stage and depth increases as the rate of nodal recurrence increases, and elective neck treatment and postoperative radiotherapy reduce the risk of recurrence. Accordingly, in patients with T2 tumors, an invasion depth of >0.5 cm, elective neck therapy can be offered as an option.

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Ethical considerations: *The study was approved by Eskişehir Osmangazi University (18.02.2020 dated and 06 numbered decision) and carried out by the Declaration of Helsinki principles and all applicable regulations.*

Author contributions: (F.T), MD: Suggesting main idea, writing part of manuscript, edition. (N.I), MD: Analyzing and interpretation of data (G.Y): Data acquisition, editing.

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