

## DIAGNOSTICS AND TREATMENT STRATEGIES OF EARLY (T1) LOWER LIP CANCER

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Communicated by Andrejs Skaģers

*Data from 35 patients were analysed to identify the main factors that may have predisposed the unfavourable clinical course in early diagnosed lower lip cancer. Of 35 patients who were sent to the Oncology Centre of Latvia, Rīga East University Hospital, with the diagnosis of early lower lip cancer, histologically diagnosis was confirmed for 22 patients. Sizes of the primary tumours were less than 2 cm (T1 size tumour). Vermilionectomy was carried out for 17 patients, wedge- or V-shaped resection was performed for 13 patients, and in five cases patients refused to receive surgical treatment and received radiation therapy instead. Review of the reports of the histological criteria for patients with aggressive course of the illness with relapses, regional metastases and also in cases of death, showed that vermilionectomy can be considered an effective diagnostic and therapeutic operation.*

**Key words:** cancer, vermilionectomy, vedge resection, recurrence.

The most common lip cancers are basal cell carcinoma (BBC) and squamous cell carcinoma (SCC). Lower lip localised cancer expresses less malignant characteristics than tumours localised in other facial areas. However, as this cancer can sometimes be overlooked, or if the diagnosis has been made late, the clinical course may turn into a worse direction. One of the believed causes leading to pathophysiological continuations of the cells is associated with prolonged actinic keratosis from prolonged effect from the sun. Indications for surgical interference may vary, but in many cases vermilionectomy has been carried out when suspecting worse gait of the tumour. The aim of the study was to identify clinical cases in which there was recurrence of the tumour and/or regional metastases, as well as cases with lethal outcome, by retrospectively analysing the factors that could have affected the unfavourable progress of the disease (diagnostic methods, tumour characteristics, treatment methods).

Patients were included in the present study if they complied with the following criteria: patient was referred to the clinic with diagnosis of lip carcinoma; patient was referred to clinic with diagnosis of actinic cheilitis and a suspicion of malignisation; patient data was available for a period of

2.4-year to 10-year follow-up; pathohistological information about size, histological subtype and TNM classification (T – size and near organ infiltration, N – lymph node metastasis, M – distant metastasis) was available. All patients underwent a thorough standard examination protocol (medical history and *status objectivus*). In addition, scrape cytology, biopsy and ultra-sonography (US) investigation was done if indicated. Clinical criteria for actinic cheilitis were desquamation of epithelium, atrophy, erosion, and unclear borders between vermilion and the skin. In cases of approved diagnosis of lower lip carcinoma, vermilionectomy was done. In addition, if after investigation with US there was suspicion of metastasis in lymph nodes or metastasis were found in one of the follow-ups, a supraomohyoid neck dissection was done to access submental, submandibular (lymph node level I), jugulodigastric, jugulo-mohyoid and anteriorly located cutaneous branches of cervical plexus and of the muscle of omohyoid lymph nodes (lymph node groups II and III). Regarding aesthetical aspects of the procedure, either an Estlander or Mucosal Advance flap (MAF) was used for wound closure. Patients were divided into two main groups based on medical history: Group I – patients with suspicious or premalignant growth, Group II – carcinoma de novo. Scrape cytology was compared to the pre-

operative or post-operative biopsy, where the biopsy was considered as the accurate one. Data were analysed on IBM SPSS Software. The Fisher's exact test was used to assess data differences between two groups of incorrect cytology based on histology and four groups between incorrect cytology in Group I and incorrect cytology in Group II separately. Significance was accepted at  $p < 0.05$ . The study evaluated 35 patients (27 males and 8 females) with suspected diagnosis of lower lip cancer, who were referred to the Department of the Head and Neck Surgery, Oncology Centre of Latvia, Rīga East University Hospital, from year 2008 to year 2010. The average age of patients was 65.4 years (min. 41 y., max. 92 y.). Based on the criteria of patient selection, three cases were excluded from the comparison of cytological and histological results; the remaining patients were divided into two groups: Group I – 13, Group II – 19. The precision of scrape cytology versus histology biopsy is reviewed in Table 1. Within each group, there were no significant differences between cytological and histological results (Group I,  $p = 0.266$ , Group II,  $p = 0.097$ ). However, there was an overall significant difference between the diagnostic methods ( $p = 0.013$ ). False negative cases in both groups were reported as an inflammation process and one false negative case from scrape cytology was perceived as a non-malignant process with no dysplastic signs. In all cases, after biopsy two main diagnoses were made: either actinic cheilitis as pre-malignant process or SCC. Size difference varied in between malignant cases (2

cm; T1) and cases with diagnosis of actinic cheilitis (3 to 6 mm).

Metastatic manifestations of SCC in regional lymph nodes were examined by US. Overall 21 patients were examined by US, and clinical changes in regional lymph nodes were detected in three patients and lymphadenectomy was performed; of these, after pathological investigation, two cases were stated as without oncological pathology in lymph nodes. Additionally, three more patients were surgically treated with lymphadenectomy due to the detection of recurrence in one of the follow up visits. Review of recurrent cases with additional treatment of lymphadenectomy is reviewed in Table 2. Average follow-up for each patient was up to 5.2 years (range 2.4 to 10 years).

Of 22 patients who had histologically confirmed carcinoma, five patients had regional metastasis, which were histologically confirmed after lymphonodectomy of the neck (22.7%). Three patients (13.6%) had regional metastases after primary surgical treatment of the tumour. In all cases metastasis was detected in submandibular lymph nodes and SOHND (supraomohyoid neck dissection) was carried out (histologically confirmed metastasis), followed by post-operative radiation therapy. Further relapses of metastases were not detected in these patients. Summing up survival rates, death due to an uncontrolled tumour occurred in one case, and in three cases the reason of death was other systemic diseases. Observation results of the patients are

Table 1. Scrape cytology comparison to biopsy

	Cytology			<i>p</i> value per group	<i>p</i> value overall
	positive	negative			
Group I (n = 13)	4	1	Positive	0.266	0.013*
	3	5	Negative		
Group II (n = 19)	14	2	Positive	0.097	
	1	2	Negative		
True negative cytological diagnosis Number of patients (%)		True positive cytological diagnosis Number of patients (%)		False positive cytological diagnosis Number of patients (%)	False negative cytological diagnosis Number of patients (%)
8 (25%)		17 (53.12%)		4 (12.5%)	3 (9.38%)

\*Grey cell indicates false cytological diagnosis in comparison with histological diagnosis

$p < 0.05$

Table 2. Review of 5 metastatic cases of lower lip SCC including case with fatal outcome

	Regional metastasis detection in follow-up (months after primary procedure)	Diameter of primary excised tumour	Thickness of primary excised tumour	Diagnoses grade of the tumour	Indention into healthy tissue (R <sub>(0 or 1)</sub> and mm)
Patient A	9	2	2.9	II	R <sub>1</sub> *
Patient B <sup>†</sup>	5	1.7	6.2	II	R <sub>0</sub> (5 mm)
Patient C	4	2	4.9	II	R <sub>0</sub> (3 mm)
Patient D	6	1.8	3.6	III	R <sub>0</sub> (5 mm)
Patient E	0**	2	3.9	II	R <sub>0</sub> (3 mm)

<sup>†</sup>Lethal outcome after 27 months related to locally invasive tumour growth infiltrated in neck vital structures

\*Intra operative frozen section reported R0. Post-operative investigation reported R1

\*\*Regional metastasis was found intraoperatively

Table 3. Review of treatments

	No. of cases	No. of recurrent cases	No. of cases dx. with regional metastasis	No. of cases associated with treating pathology	No. of death cases not-associated with current pathology
Radiation therapy	5	1*	1*	1*	1
V resection	11	–	2	–	1
Vermilionectomy	6	1	–	–	1

\* Patient who died from the disease – Patient B (Table 2)

shown in Tables 2 and 3 (in cases of relapses and metastases).

All patients receiving lymphadenectomy had Grade II or higher tumour stage. In one case resection lines were positive, where in this case the intra-operative frozen section showed no evidence of tumour invasion, but further histological analysis post-operatively showed positive resection lines (patient A, Table 2). In one case SOHND was conducted in the same procedure when the tumour was resected (patient E, Table 2).

In case of disease-associated death, the patient received radiation therapy and recurrence was noted in the 5<sup>th</sup> month follow-up. V resection was performed to control the recurrent growth. In post-operative histology examinations, the tumour was defined as Grade III. After nine months, metastasis was found in the submandibular and submental region, on which basis SOHND was carried out and post-operative radiation therapy applied. In lymphadenectomy, one submental and two submandibular lymph nodes were specified with extracapsular metastatic growth and one upper jugular group lymph node was with no capsular breach. Radical neck dissection was indicated after 12 months when metastasis was found in middle jugular group. After 2.4 years, patient B (table 2) died from local neck vital structure failure.

Radicality of the surgeon's approach is defined by characteristics of the tumour. Features describing lower lip cancer in particular still have some flaws — prognostic factors, treatment efficacy, clear guidelines for surgical protocol, etc. Five-year survival rates are defined as the main attribute that describes the long-term prognosis of the tumour. Studies have reported that the five-year survival rate of lower lip cancer with cancer T stage of I to varies from 68.3% to 84.5%, with some studies drawing a direct link to pre-cancerous process of actinic cheilitis (Schüller *et al.*, 2015; Ozkul *et al.*, 2016). Pathology-associated death in case of lower lip cancer is usually due to metastatic tumorous formations in physiologically crucial neck organs. Most studies report a rate of metastasis reaching up to 2% (Cabello *et al.*, 2015). In the present study, only 19 patients completed a five-year follow up course, due to reasons associated with death by natural cause or inability to contact certain patients. Of 19 patients, one death was associated with the studied pathology and the five-year survival rate was calculated to be 94.7% for grade I tumour. Of 19 patients, three patients were reported with metastatic lesions in regional lymph nodes reaching the rate of metastasation up to 15.8%.

Scrape cytology versus histology has been reported to differ in precision, but in duration of time and invasive approach, cytology is a less aggressive diagnostic approach. The lack of precision in scrape cytology is due to the way the cell material is obtained, as it leads to disruption of cell architecture, traumatization, and lack of border navigation. Most patients in the present study received pre-surgical cytology and post-surgical histology evaluation, where afterwards treatment methods were analysed based on the histology diagnosis. Evaluating treatment methods as a whole, statistical significance ( $p < 0.05$ ) was acquired in favour of histology. While evaluating groups with different pre-diagnostic state (either pre-cancerous or de novo) statistical significance was not found. This may be due to the low number of patients in each group, where in the whole treatment evaluation patient groups were larger. At the end, either it was de novo group or that with suspicion of actinic cheilitis, patients treated surgically did not differ from cytology diagnostic conclusions.

Treatment in cases of lower lip cancer or pre-cancerous stage has been discussed extensively. Van der Wal (1996) concluded that either surgical approach is potentially safe in terms of development of recurrent growth by primary tumour when it is 3 mm or less. De Visscher *et al.* (2002) hypothesised safe healthy tissue indentation to be the factor of recurrent development, where the safe healthy tissue indentation is less than 3 mm, if an intra-operative frozen section was made and considered to be adequate. In the present study, two patients were diagnosed with recurrent growth after a five-month follow-up. In both cases the tumour thickness was more than 3 mm and the primary treatment method was chosen to be vermilionectomy. Secondary treatment for more recurrent growth was by local excision with the V resection surgical approach. While surgical treatment in terms of healthy tissue indentation was set to be 3 mm in cases of V resection, no recurrence was detected in the follow-ups (Hjortdal *et al.*, 1995).

Functional and aesthetical balance is the ultimate goal for surgical tumour excision and reconstruction. In cases of lower lip cancer, the most aesthetical and functional balance was achieved by MAF after vermilionectomy (Sand *et al.*, 2010). In cases of elderly patients with side-effects, direct closure proved to be more sufficient. In all cases of vermilionectomy in the studied cases, reconstruction with MAF was conducted.

A controversial issue is the treatment approach when clinical signs of metastasis are not found, because micro metas-

tasis is important in late diagnosis of lymph nodule tumour invasions. Possible treatment options are prophylactic lymphadenectomy, prophylactic radiation therapy, or wait-and-see policy, which was the chosen option in the studied cases. Even though literature reports a statistically low chance of metastatic lower lip cancer, early stages with metastasis (T1) have been reported. Kahlil *et al.* (2008) in a clinical experiment evaluated the efficiency of sentinel node biopsy as a prophylactic diagnostic method, where micro metastasis was found in one case of 14. In the present study, SOHND was performed only in cases with a US atypical lymph node, where tumour metastasis was found in only one case. The efficiency of SOHND in controlling regional metastasis in cases of lower lip carcinoma was found to be safe and with good prognosis for level I lymph node control if post-operative radiation therapy was carried out according to indications. (Gooris *et al.*, 2002).

In all the cases metastases occurred in submandibular lymph nodes and SOHND was carried out, followed by post-operative radiation therapy. Further relapse of metastases was diagnosed in one patient. After 12 months, metastases were discovered in a middle jugular group, and due to this RND (Radical Neck Dissection) was carried out, but it was not effective.

Lip cancer can be life-threatening in the early stages in cases of inadequate diagnostics and treatment approach. Histological examination plays a major role in making the diagnosis, especially in cases when the tumour develops on a pre-cancerous background (actinic cheilitis). In some cases, vermilionectomy (if the tumour is less than 3 mm thick — micro invasive carcinoma) is not only an efficient diagnostics, but also a treatment procedure. In cases of occult regional metastases, as well as in cases of clinically enlarged regional lymph nodes, sentinel lymph node biopsy can be crucial for making the right decision, whether to perform prophylactic or therapeutic neck lymphonodectomy. SOHND is considered to be an efficient operation in cases of level I positive regional lymph nodes. In the present article we did not review nor propose new treatment approach strategies in cases of lower lip cancer. However, attention was brought to a wider scope of actinic cheilitis and ap-

proach to lower lip cancer diagnostics in cases when symptomatic characteristics are not clearly evident. Although in the present offered guidelines no radical diagnostic approach has suggested, in these cases it would bring more weight to the final diagnosis.

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Received 18 December 2017

Accepted in the final form 17 October 2019

## AGRĪNA APAKŠLŪPAS VĒŽA (T1 ) DIAGNOSTIKAS UN ĀRSTĒŠANAS STRATĒGIJA

Lai gan apakšlūpas vēzis, salīdzinot ar citu mutes dobuma gļotādas lokalizāciju ļaundabīgiem audzējiem, tiek uzskatīts par mazāk agresīvu, tomēr reizēm, neraugoties uz savlaicīgi uzsāktu ārstēšanu, tā klīniskā gaita ir nelabvēlīga. Nereti apakšlūpas vēzis attīstās uz ilgstoši norisošas aktīniskās (solārās) keratozes fona, kura var aptvert ievērojamu apakšlūpas sārtās daļas rajonu, kas reizēm diktē nepieciešamību veikt plašākas ķirurģiskās manipulācijas ne tikai ārstniecisku, bet arī diagnostisku indikāciju dēļ. Lai izvērtētu lūpas vēža diagnostisko metožu (klīniskās izmeklēšanas dati, nokasījuma citoloģija, biopsija, ultrasonogrāfija) precizitāti, ārstēšanas veida efektivitāti (vermilonektomija, rezekcija, staru terapija), veicām retrospektīvu pētījumu. Pētījuma uzdevums bija, identificējot gadījumus, kad tika konstatēti audzēju recidīvi un/vai reģionālas metastāzes, kā arī gadījumus, kad pacienti mira no nekontrolēta audzēja, analizēt faktorus, kuri varēja ietekmēt slimības nelabvēlīgo norisi. Pētījuma grupā tika iekļauti 35 pacienti laikposmā no 2008. līdz 2010. gadam, kuri tika atsūtīti uz Rīgas Austrumu klīniskās universitātes Latvijas Onkoloģijas centru ar diagnozi apakšlūpas vēzis vai aizdomas par apakšlūpas vēzi. Karcinomas gadījumos (22 pacienti) primārā audzēja izmēri nepārsniedza 2 cm un atbilda T1 audzēja izmēriem. Analizējot diagnostisko un ārstniecisko metožu rezultātus, secinājām, ka lūpas vēzis agrīnā stadijā var būt dzīvību apdraudoša saslimšana neatbilstošas diagnostiski ārstnieciskās taktikas gadījumos. Viens pacients mira sakarā ar slimības recidīvu un tālāku reģionālu metastazēšanos. Vermilonektomija atsevišķos gadījumos (ja audzēja biezums nepārsniedz 3 mm – mikroinvazīva karcinoma) uzskatāma ne tikai par efektīvu diagnostisku, bet arī ārstniecisku procedūru. Pieciem pacientiem vermilonektomiju varējām uzskatīt kā definitīvu vēža ārstēšanu. Vienā gadījumā pēc vermilonektomijas attīstījās recidīvs, bet turpmāka apakšlūpas rezekcijas operācija novērsa tālāku audzēja izplatīšanos. Izvērtējot gan kakla limfonodulektomijas veikšanas nepieciešamību, gan tās apjomu, ir nepieciešama efektīvāku diagnostisko metožu ieviešana klīniskajā praksē. Rakstā netiek piedāvātas jaunas ārstēšanas metodes, bet skaidrāk tiek definēts diagnostiski ārstniecisko metožu pamatots pielietojums, it īpaši gadījumos, kad apakšlūpas patoloģisko izmaiņu simptomātika uz aktīniska heilīta fona nav pārliecinoša. Radikālas diagnostikas metodes šajos gadījumos ir ievērojami informatīvākas un agrīnu ļaundabīgu izmaiņu gadījumos uzskatāmas par pamatotām ārstnieciskām metodēm, kas līdz šim pasaules literatūrā netiek skaidri definētas.