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Primary surgical treatment versus salvage surgery: Results of free flap reconstruction performed in 100 patients with oropharyngeal cancer

Jacek Banaszewski*, Maciej Pabiszczak, Andrzej Balcerowiak, Tomasz Pastusiak, Agata Andruszko

Department of Otolaryngology, Poznan University of Medical Sciences, Przybyszewskiego Street 49, 60-355, Poznań, Poland

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ABSTRACT

This research sought to analyze the functional results of free flap reconstruction in two groups of patients with head and neck cancer: first group started with radiochemotherapy followed by reconstructive surgery, second group underwent initiative surgery.

Materials and methods: In a group of 100 patients, surgery was used as the primary form of treatment in 55 (55%) patients, and the remaining 45 patients (45%) had chemoradiotherapy introduced first. Statistical analysis was performed with Statistica v. 12. The chi-square test and test of proportion were used for categorical data. Student's t-test was used for continuous data. Probability of survival was calculated using the Kaplan–Meier method where the censoring variable was time to death. To compare survival between cohorts, we used the Cox's test. The level of significance was set at $p < 0.05$.

Results and conclusions: Initial radiochemotherapy prior to surgical treatment indicated an increased risk of local tumor recurrence, flap degeneration, and other local complications.

1. Introduction

Oropharyngeal carcinomas account for 3% of all malignant cancers [1]. Reconstructive surgery in this anatomical region is always a challenge, for it affects breathing, swallowing and speech ability. There is also an esthetic aspect, which has to be put into account. In general, surgical treatment is recommended for cancers of the oral region, whereas chemoradiotherapy (CRTH) is the favored treatment for pharyngeal cancers [2,3]. Tumor's size and bone infiltration also determine the choice of the first treatement [4]. When there is a possibility of organ preservation, there is a trend toward referrals for CRTH as the initial method of treatment. Tumor resection combined with reconstruction is necessary in advanced cancer stages or the possibility of tumor recurrences. Currently, the reconstructive technique involves a free tissue graft with microanastomosis and tissue islands that are dependent on the extent of tissue loss (skin, muscle, bone). The workhorse flaps used in head and neck region are the radial forearm, anterolateral thigh, and fibular free flaps.

Our research aimed to analyze data obtained during the course of treatment of patients with head and neck tumors post immediate free-flap reconstruction. An emphasis was placed on the investigation of the functionality of the free flaps and the basic parameters of the treatment. The results were compared among the patients who were primarily treated with CRTH prior to surgery and those with surgery first.

2. Materials and methods

A retrospective analysis of 100 patients who underwent free flap reconstruction after surgical removal of primary or recurrent tumor at the Department of Otolaryngology, Poznan University of Medical Sciences, was conducted. During a five-year period ranging from 2007 to 2011, 125 patients were included into the study. However, data from 25 patients could not be collected due to the patient's neglecting the follow-up, 100 patients were evaluated. In all cases (primary and recurrent tumor), histopathological examination revealed squamous cell carcinoma (SCC). Primary surgical treatment was performed on 55 (55%) of the patients, while the remaining 45 patients (45%) underwent salvage surgery following CRTH. Primary nonsurgical treatment was performed by radiochemotherapy: intensity-modulated radiation therapy (IMRT) - 1.8–2.0 Gy/d fractions, Monday to Friday for a total dose 62–72 Gy combined with cisplatin. At the time of treatment, the patients' age varied from 25 to 75 (mean 57.5, median 58, SD- 9.2), with 77 male patients (77%) and 23 female patients (23%). Primary tumors were most frequently located in the oral cavity 63 (63%), oro-

* Corresponding author.
E-mail addresses: jbanasz@ump.edu.pl, otosk2@ump.edu.pl (J. Banaszewski).

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Table 1
Range and type of reconstruction with free flaps in patients treated during 2007–2011.

Reconstruction Range		Type of Reconstruction		
Anatomical Structure	Number of Patients n = 100	RFFF Acquired from a forearm flap n = 66	ALT Antero-Lateral Thigh Flap n = 32	Fibular Flap n = 2
Simple anatomical structure				
Tongue	9 (9%)	5 (7,6%)	4 (12,5%)	
Buccal Region	5 (5%)	3 (4,5%)	2 (6,3%) (double-island)	
Hypoharynx	7 (7%)	6 (9,1%)	1 (3,1%)	
Multiple anatomical structures				
Tongue and Floor of the Mouth	45 (45%)	34 (51,5%)	11 (34,4%)	
Hypoharynx and Esophagus	11 (11%)	8 (12,1%)	3 (9,4%)	
Oropharynx	12 (12%)	5 (7,6%)	7 (21,9%)	
Maxillo-Ethmoidal complex	3 (3%)	2 (3%)	1 (3,1%)	
Floor of the mouth, mandible	1 (1%)			1 (50%)
Floor of the mouth, skin of the neck	3 (3%)	–	2 (6,3%) (double-island)	1 (50%)
Oropharynx and Parotid Gland	4 (4%)	3 (4,5%)	1 (3,1%)	

Table 2
Functional results after 1 year after reconstructive surgery with RFFF, ALT and fibula flaps.

Anatomical Structure	Number of Patients n = 100	RFFF n = 66	Aspiration (A) without tracheotomy	Swallowing (S) without gastrostomy or nasogastric tube	A+S
Simple anatomical structure					
Tongue	9 (9%)	5 (7,6%)	5 (7,6%)	5 (7,6%)	5 (7,6%)
Buccal Region	5 (5%)	3 (4,5%)	3 (4,5%)	3 (4,5%)	3 (4,5%)
Hypoharynx	7 (7%)	6 (9,1%)	5 (7,6%)	6 (9,1%)	4 (6,1%)
Multiple anatomical structures					
Tongue and Floor of the Mouth	45 (45%)	34 (51,5%)	34 (51,5%)	34 (51,5%)	34 (51,5%)
Hypoharynx and Esophagus	11 (11%)	8 (12,1%)	5 (7,6%)	5 (7,6%)	5 (7,6%)
Oropharynx	12 (12%)	5 (7,6%)	5 (7,6%)	5 (7,6%)	5 (7,6%)
Maxillo-Ethmoidal complex	3 (3%)	2 (3%)	2 (3%)	2 (3%)	2 (3%)
Floor of the mouth, mandible	1(1%)				
Floor of the mouth, skin of the neck	3 (3%)	–			
Anatomical Structure	Number of Patients n = 100	ALT n = 32	Aspiration (A) without tracheostomy	Swallowing (S) without gastrostomy or nasogastic tube	A+S
Simple anatomical structure					
Tongue	9 (9%)	4 (12,5%)	3 (9,4%)	2 (6,3%)	2 (6,3%)
Buccal Region	5 (5%)	2 (6,3%) (double-island)	2 (6,3%)	2 (6,3%)	2 (6,3%)
Hypoharynx	7 (7%)	1 (3,1%)	1 (3,1%)	1 (3,1%)	1 (3,1%)
Esophagus	3 (3%)	–			
Multiple anatomical structures					
Tongue and Floor of the Mouth	45 (45%)	11 (34.4%)	9 (28,1%)	7 (21.9%)	7 (21.9%)
Hypoharynx and Esophagus	11 (11%)	3 (9,4%)	2 (6,3%)	3 (9,4%)	1 (3,1%)
Oropharynx	12 (12%)	7 (21.9%)	6 (18,8%)	5 (15,6%)	5 (15,6%)
Maxillo-Ethmoidal complex	3 (3%)	1 (3,1%)	1 (3,1%)	1 (3,1%)	1 (3,1%)
Floor of the mouth, skin of the neck	3 (3%)	2 (6,3%) (double-island)	2 (6,3%)	1 (3,1%)	1 (3,1%)
Multiple anatomical structures	Number of Patients n = 100	Fibula n = 2	Aspiration (A) without tracheostomy	Swallowing (S) without gastrostomy or nasogastic tube	A+S
Floor of themouth, mandible	1 (1%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)
Floor of the mouth, skin of the neck	3 (3%)	1 (50%)	1 (50%)	1 (50%)	1 (50%)

and hypopharynx 27 (27%), spreading to surrounding regions such as maxilloethmoidal complex 3 (3%), upper part of the esophagus 3 (3%), and parotid gland 4 (4%) [Table 1]. All patients underwent physical examination and diagnostic imaging (magnetic resonance imaging - MRI, computer tomography - CT, ultrasound examination) to determine the tumor extent and to evaluate lymphatic system involvement. Viability of the vascular supply of the donor site was performed in all cases. Allen's test was used for radial forearm flap (RFFF), CT angiography or MRI for the free fibular flap, and Doppler ultrasound (Bidop, Hadeco) for the identification of musculocutaneous perforators in anterolateral thigh flap (ALT). Seven patients had post-op complications: flap decay (3 cases) and local tumor recurrence (4 cases); subsequent surgical procedures were performed. Seven secondary reconstructions were performed to correct the free flap failure with either radial forearm flap (4 cases) or anterolateral thigh flap (3 cases). Additionally, one patient (1%) required two free flaps (radial forearm free flap [RFFF] and ALT) due to the extensive size of the defect after tumor excision. RFFF was chosen in 66 cases (66%), while anterolateral flap (ALT) was used in 32 (32%) of patients [Fig. 2]. Marginal resection of the mandible was executed in 25 cases (26.8%), whereas 2 patients (2%) had en-bloc

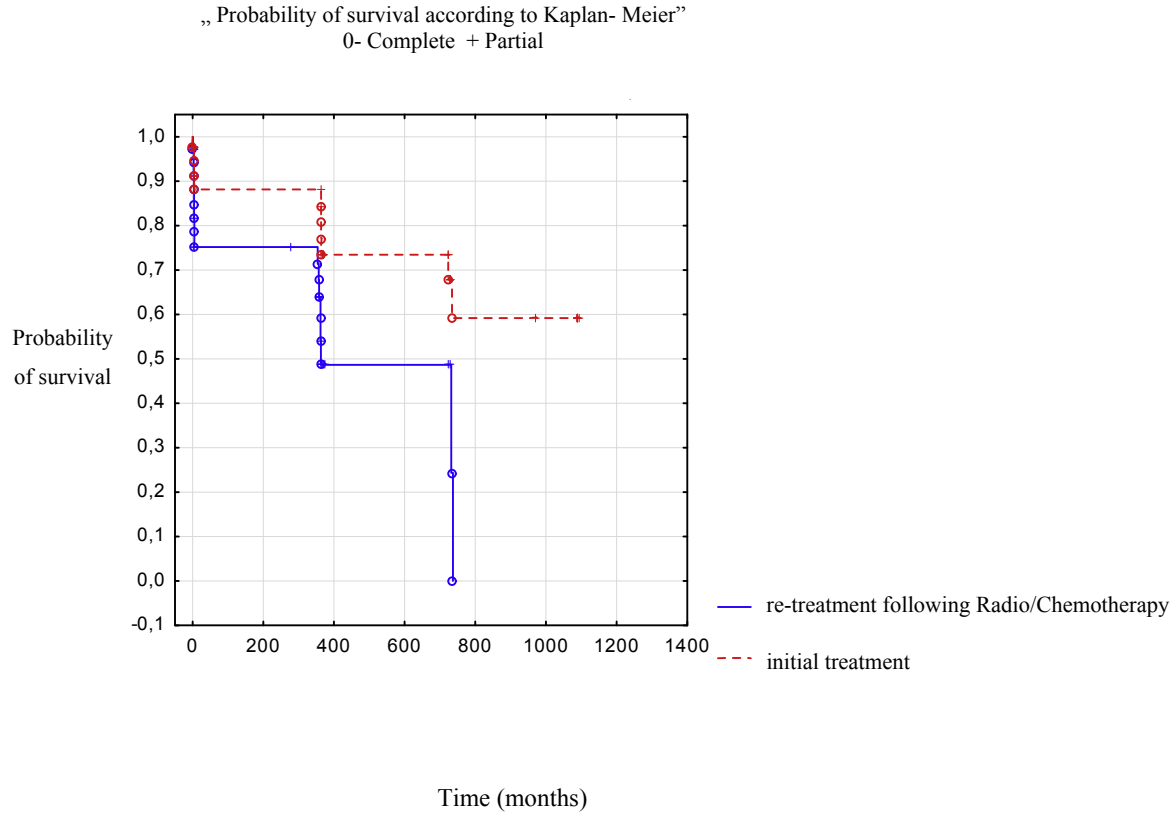

Fig. 1. Survival curve presenting primary surgery and following radiochemotherapy according to Kaplan Meier Analysis.

resection of the mandible and reconstruction with the osteocutaneous free fibular flap [Fig. 3]. Prior to surgery, 46 (46%) patients had a Percutaneous Endoscopic Gastrostomy (PEG) inserted; the rest 54 (54%) patients were temporarily fed through a nasogastric tube. All patients had pre- and postoperative consultation and follow up by a speech therapist to master swallowing and intelligible speech again.

Functional examination of the patient's swallowing, breathing, and speaking was evaluated one year after the surgical procedure. A positive result was assigned to patients who breathed without the need for tracheostomy, had oral food intake (constant and liquid diet), and with intelligible speech [Table 2]. Statistical analysis was performed using Statistica v. 12. The chi-square test and test of proportion were used for categorical data. Student's t-test was used for continuous data. Probability of survival was calculated using the Kaplan–Meier method where the censoring variable was the time to death. To compare survival between patients treated initially and re-treated following CRTH, we used the Cox's test. The level of significance was set at $p < 0.05$.

3. Results

We compared: healing, hospitalization time and oncologic results of the primary surgical treatment and salvage reconstructive treatment.

3.1. Healing

In both groups (100 patients), good primary healing occurred in 67 patients (67%), while infectious wound complications occurred in 33 patients (33%). In the latter group, 15 patients (15%) had local wound infection with a salivary fistula on the neck, which required surgical intervention. Six patients out of the whole group (100) required an immediate revision of the anastomoses within the first 48 h, due to ischemic changes. There were 5 (5%) patients with free flap failure. Statistical analysis revealed a significant difference in healing between the primary and salvage surgery groups ($p = 0.00508$). Comparison of both groups revealed that out of 55 patients treated primarily with surgery, 42 patients (76.4%) healed correctly, whereas in the CRTH group, 18 patients (40%) presented with signs of disturbed wound healing. There was no statistically significant difference between local healing and level of tumor extent, age and sex of the patients: $p = 0.78421$, $p = 0.42839$ and $p = 0.14526$, respectively. Statistical analysis revealed a value of ($p = 0.00508$). Among 6 patients in whom reanastomosis was performed, the intervention was performed in 2 patients after primary operation and in 4 patients after salvage.

3.2. Hospitalization time

The average time of hospitalization was approximately 31 days (median = 27 days). There was no significant difference between hospitalization time of patients who were primarily treated with surgery (mean = 30 days) and those who have first underwent CRTH (mean = 31 days).

3.3. Functional results

The best functional results were noticeable in patients who underwent one site anatomical, simple reconstruction (e.g. tongue or base of the oral cavity) and more complex anatomical restoration (e.g. tongue and base of the oral cavity; tongue and pharyngeal wall) using RFFF. Sixty one (92.4%) patients with RFFF reconstruction showed good rehabilitation of oral swallowing, and their tracheotomy was closed. The poorest outcome was observed in patients who had reconstructive surgery of multiple anatomical structures (e.g. tongue and base of the oral cavity; tongue and pharyngeal wall) using ALT. Among 32 patients, only 22 (68.7%) successfully reeducated oral swallowing and started to breath without tracheotomy [Table 2]. All (66 [100%]) patients who underwent reconstruction with RFFF and 59% (19) who had ALT flap showed intelligible speech.

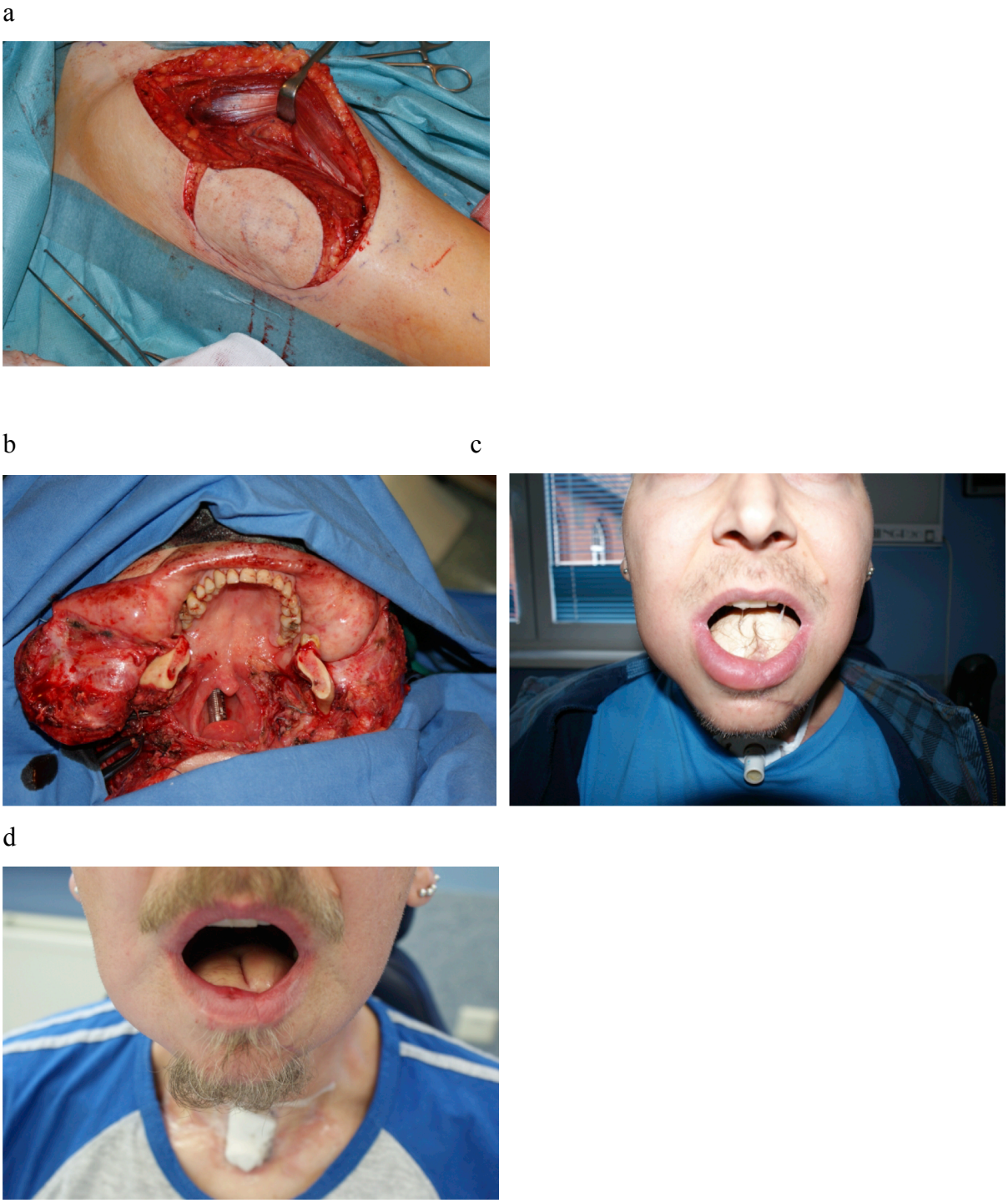

Fig. 2. Harvest of free anterolateral thigh flap with vascular pedicle (a) loss after resection (total glossectomy with partial resection of the mandible) of huge recurrence cancer of the tongue (b) 3 weeks after reconstruction with ALT flap and titanium plates (c) 2 months post operation, without tracheostomy (d).

3.4. Oncological results

The overall analysis of oncological results in the whole group of 100 patients showed: local recurrence in 68 (68%) and neck lymph node metastasis recurrence in 21 patients (21%). Thirty-nine patients (39%) died: 7 (17.9%) due to diffuse neck lymph node recurrence, 28 (71.8%) due to local recurrence and 4 (10.3%) because of distant metastasis. The follow-up period varied from 12 to 48 months.

The 12-month survival rate was attained in 70% patients without tumor recurrence. Increased frequency of local recurrence was observed in 19 patients (42.2%) who had CRTH, in contrast to the group of patients primarily treated with surgical intervention (5 patients (9.1%)). However, there was no significant difference between local recurrence (T) and sex or age of the affected individuals ($p = 0.67381$ and $p = 0.34728$, respectively). The 2- year survival rate was achieved in 54 (54%) of patients. The Kaplan-Meier analysis showed that primary surgical intervention was significantly more effective than salvage surgery. Primary surgical treatment provided patients with an increased probability of 2-year survival (60%), whereas those treated by salvage surgery (50%), $p = 0.01558$ [Fig. 1]. 3- year survival rate in 28 of

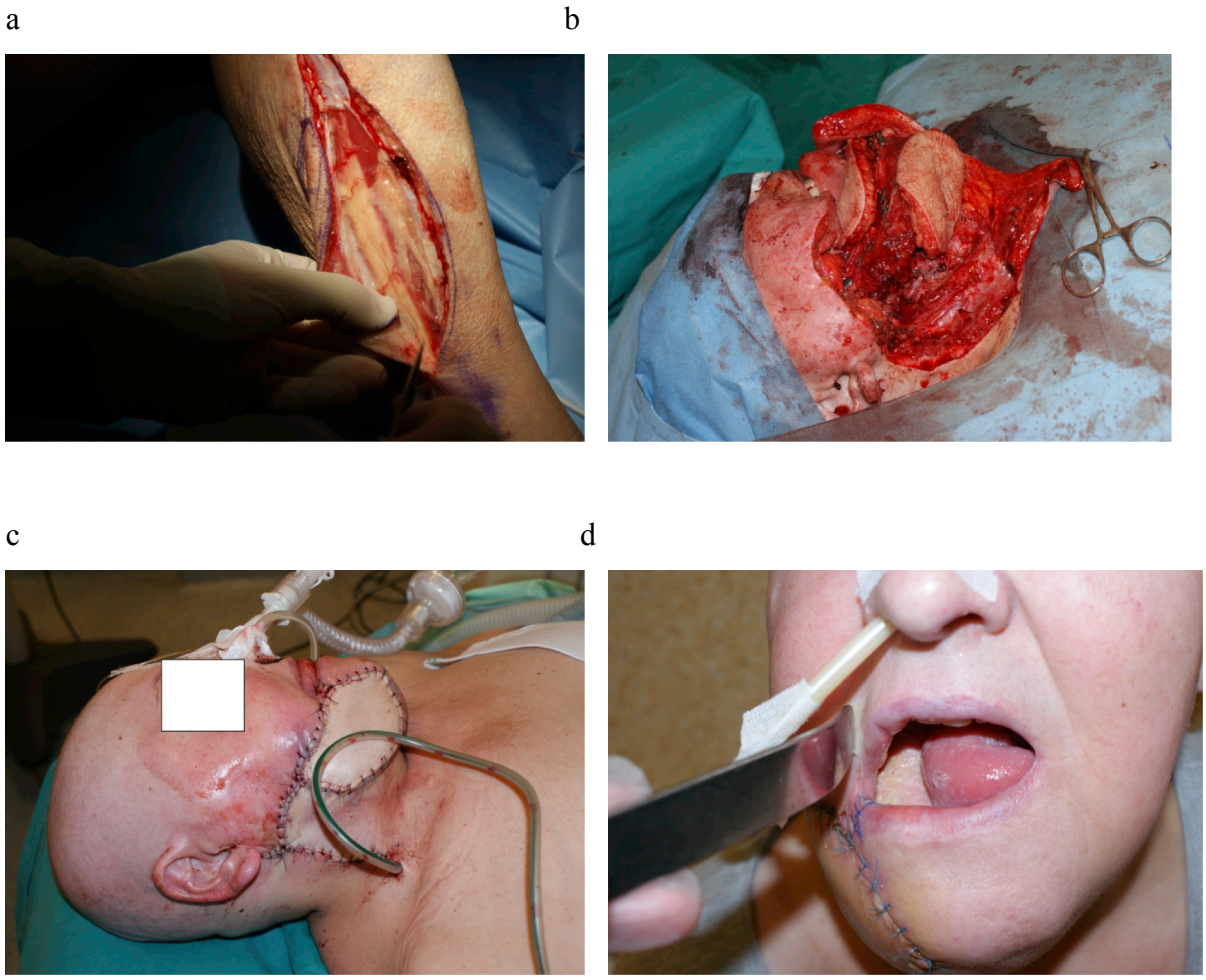

Fig. 3. Harvest of free fibula flap (a) reconstruction with fibula osteo-cutaneous free flap with 2 skin islands (for skin and oral mucous reconstruction) of loss after resection of recurrence of the floor of the mouth with infiltration of the mandible (b) postoperative view (c) 2 weeks post operation (d).

patients was obtained (28%). A significant difference was observed between patient survival and incidence of local recurrence ($p = 0.00000$) as well as between patient survival and metastasis to the lymphatic system of the neck ($p = 0.02069$). No significant difference was observed between survival and degree of cancer advancement (T), age, and sex of the patients ($p = 0.64072$, $p = 0.10258$, and $p = 0.47106$, respectively).

4. Discussion

Surgical resection of widely spread tumors within the oropharyngeal region followed by reconstruction presents a significant challenge to both resective and recontructive surgical teams [5]. Tumor infiltration and evaluation of excision during surgery is worse in patients with previous CRTH treatment. Decision regarding the type of reconstruction is made prior to surgical treatment based on laryngological examination, CT, MRI, PET and neck ultrasound. In patients with uncertain vascular competency, the diagnosis was expanded to precisely determine the donors site, and angiography, ultrasound Doppler, and Allen test were carried out according to the proper preoperative protocol [6,7].

Reconstruction of the majority of defects within the region of the hypopharynx, esophagus, and cheek, but mostly within the ventral part of the tongue as well as floor of the mouth was performed with RFFF (68%). According to the literature, the prevalent usage of this flap is performed in case of tongue defects, which not exceed 70%. This type of flap technique allows to obtain good functional results [8]. The main advantage is the pliability of acquired tissues and capability of various shape attainment [9,10].

Due to large surface volume, the anterolateral thigh flap (ALT) was used in more extensive reconstructions: base and body of the tongue, defects following total parotid gland removal and floor of the mouth defects along with skin resection or full - thickness buccal region [Fig. 2]. In one case, a double island flap was created to close an intraoral defect and to cover external cutaneous defects. Implementation of anterolateral thigh flaps was presented by various authors [11,12].

The average age of patients was 56 years; the youngest patient was a 24-year-old male, and the eldest was 75 years old. No age limitation was imposed during pre-qualifying the patients for surgery. Advanced age is not a surgical contraindication, and it has no apparent negative effect on treatment outcomes [13,14]. Final result is determined by an overall health status of the patient, and the current viability status of vascular circulation determines the efficiency of the pedicle [21]. Age played no significant role in patient survival, risk of local recurrence, and healing.

In 28% of patients, postoperative complications led to healing by secondary intention. Wound infections after reconstructive procedures varies between 26%-48%, despite perioperative antibiotic therapy [15]. Dysphagia, fasting, protein deficit, cachexia, and increased risk of local infections subsequently led to worse healing and fistula formation. Our statistical data indicate that the process of healing was significantly better for those who underwent primary surgery when compared with groups treated primarily by CRTH ($p = 0.00508$). These observations are confirmed by other authors [15]. In the last few decades, primary

CRTH has been used because of its organ salvage potential [16]; nonetheless, local recurrences are challenging to track in the early stages and lack of proper early diagnosis can lead to extensive tissue defect that require salvage surgery. Post radiation changes make macroscopic diagnosis of tissue margins difficult, inadvertently increasing the risk of additional local recurrences. Tsou et al. [17] confirmed nearly 2.5 times higher risk of fistula formation in patients treated surgically following primary chemotherapy, while Chen et al. [18] reported that in 5%–25% patients, surgical re-intervention was necessary following the first week of treatment. Additionally, radiotherapy has shown an increased risk of local hematoma and thrombophlebitis.

In 4 of 7 (71%) patients after salvage surgery, the most frequent direct cause of flap necrosis was an extensive thrombosis due to vascular atherosclerosis of flaps pedicle or the artery from microanastomosis. It is accepted that complications involving flap rejections mainly coincide with general diseases, primary CRTH, affected margins and metastasis to lymph nodes of the neck [19]. However, the most important factor increasing the risk of flap failure is radiotherapy, which could lead to endothelial inflammation and subsequent increased risk of thrombophlebitis [20,21].

Our data indicated flap survival of 95%. Within the initial 48 h following surgical intervention: 6 patients experienced a lack of proper circulation in the flap and one patient exhibited pallor of the flap, which indicated failure of arterial anastomosis. Five patients presented with bruising of the flap, which indicated failure of venous circulation.

The proportions of these types of complications are confirmed by other authors, and failure of arterial anastomoses remains the most frequent cause of complications within the first 48 h following the treatment. Bozikov and Arnez [19]" reported flap healing on a similar level approaching 94%". Similar results were obtained by other authors [20].

Functional results are difficult to estimate and to compare especially in such heterogenic group of patients (location and the extent of the tumor). In our experience the quality of life improves significantly when the patient starts to swallow constant and liquid food without additional help (gastrostomy). Speech intelligibility is also important in social independent life and can be achieved with permanent tracheotomy, which is unacceptable by some patients. Our functional data collected after one year of rehabilitation were similar to those of other authors [22–24].

Survival rate is difficult to compare especially among a diverse group of patients such as in this study (different regions, different primary treatments); however, such comparison allows assessing the patient's likelihood of survival after the treatment.

In the present study, the overall survival rate differential of those treated due to extensive tumors of head and neck with free flap reconstruction indicate a significant decline throughout the observation period: during 18 months, the survival rate was 75%, and after 48 months, the rate was 54.2%. Statistically, primary surgery showed increased favorable outcome of treatment when compared with salvage surgery ($p = 0.001558$). Dequanter et al. [25] reported similar unfavorable results obtained by salvage surgery in those at T3 and T4. Therefore patient qualification for surgical treatment should be based upon extension of local recurrences and not based solely on technical reconstruction of a removed organ. Gleich et al., [26] suggest the probability of an unfavorable treatment outcome in those diagnosed with rT3 and rT4 stage.

5. Conclusion

To summarize, resection with free flap reconstruction is the only effective treatment method in patients with extensive cancer of the oropharyngeal region. Surgical treatment following primary CRTH is characterized by a significantly increased risk of local tumor recurrence, free flap decay and other local complications.

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