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Outcomes of postoperative radiation therapy in fibular free flap reconstruction for head and neck cancer

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Abstract

In the treatment of an advanced stage head and neck cancer, additional therapeutic modalities are often combined with surgery. The timing of surgery in relation to other treatment modalities, such as radiation or chemoradiation therapy, remains a topic of continuous discussion. In this study, a series of 13 patients who underwent segmental mandibulectomy followed by postoperative irradiation or chemoradiation at Turku University Hospital between 2011 and 2018 was analyzed. Radiation therapy was scheduled from five to twelve weeks after the surgery. All 13 fibular reconstruction flaps remained viable at the last follow-up. In general, the outcomes of these patients` fibula grafts were consistent with results published by other institutes. It was concluded that postoperative irradiation does not have a negative impact on the survival of microvascular fibular flaps. However, postoperative radiation therapy appeared to increase late complications in the grafts.

Key words: HNSCC, Fibular free flap, Mandibular reconstruction, Postoperative irradiation/chemoradiation

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Introduction

Head and neck cancers represent a heterogeneous group of tumors located in the head and neck region. 90% of head and neck cancers are histologically classified as squamous cell carcinomas. The primary subsites of head and neck cancers are the lip and oral cavity, oropharynx, nasopharynx, hypopharynx, sinonasal area, larynx and upper esophagus. In 2-5 % of cases of head and neck squamous cell carcinomas, the primary site remains unknown. (1) Treatment of head and neck cancers typically involves surgery, radiation therapy, chemotherapy or a combination of these modalities. In the case of early-stage HNSCCs, single-modality treatment is often sufficient, while more advanced stages generally require combined therapeutic approaches. Immunotherapy has emerged as a promising treatment option for recurrent or metastatic HNCs, offering new avenues for management.

The prognosis for patients with head and neck cancers has improved significantly over the past 40 years. There have been advancements in oncological treatments, particularly in radiation therapy and chemoradiotherapy. A major breakthrough occurred in the 2000´s with the introduction of intensity-modulated radiation therapy (IMRT). IMRT allows for precise radiation targeting to the desired area and modulates the radiation dose. This improves treatment effectiveness while minimizing radiation exposure to healthy tissues, thus reducing the side effects of radiation therapy. However, surgery remains the cornerstone of treatment for cancers that have invaded bone, as radiation therapy is ineffective for these tumors. The tumor is usually removed in one block, following anatomical boundaries and ensuring a sufficient margin of healthy tissue. If necessary, cervical lymph node dissection is also performed. Vascularized bone-muscle-skin flaps have replaced other methods for reconstruction after segmental mandibulectomy. Over past few decades, the fibula has become the preferred donor site for these flaps. (2) From a surgical perspective radiation therapy with cytotoxic agents gives an additional challenge for blood supply, flap survival, wound healing and the surgical technique employed. These challenges are different depending on the combination of the treatment.

The aim of this study is to analyze the surgical outcomes of mandibular reconstructions performed at Turku University Hospital between 2011 and 2018, where postoperative radiation therapy was used as adjunctive treatment following surgery, in contrast to the preoperative radiation therapy that was administered before 2010. The comparison is made with a previous study conducted by Irjala et al. at Turku University Hospital in 2011, which examined surgical outcomes for patients treated between 1999 to 2006, when radiation therapy was administered before surgery. (3)

Patients and methods

We performed a retrospective analysis of the medical records of all patients who underwent segmental mandibulectomy and reconstruction with a vascularized free bone flap from the fibula, followed by postoperative radiation therapy, between January 1st, 2011, and December 31st, 2018, at Turku University Hospital, Finland. We excluded patients who had previously undergone radiation therapy to the head or neck region from our study. For all included patients, the fibula reconstruction surgery was performed as the primary operation for their head and neck cancer.

Of the patients included in the study, we analyzed the patient`s age, comorbidities, diagnosis leading to surgery and classifications of the cancer being treated. Additionally, the type of reconstruction, flap viability, and surgical outcome, including dental implants, were assessed.

Results

During the selected time period, 13 patients fulfilled the inclusion and exclusion criteria and were included in this study. Four of the patients were women and nine were men. The ages ranged from 33 to 82 years. Eight patients were current or former smokers, while the remaining five had never smoked. All the patients were operated due to squamous cell carcinoma. Eight of the carcinomas were gingival origin, two from baseos oris, two buccae and one from the retromolar area. All the carcinomas were of an advanced stage tumor. The TNM classification and the grade of the tumors are shown in Table 1.

A microvascular bone flap from fibula was the primary reconstruction for all the patients. Five patients had complications of the flap after the operation. Only one patient, #9, experienced a post-operative primary complication, which was infection and fistula at surgical site. The complications related to the graft in the other four patients occurred between 2 and 12 months after the operation. In patient #2 the skin portion of the graft was necrotized and part of it was lost. Additionally, about a month after the completion of chemoradiation therapy, fistulization occurred at the skin site and a segment of the bone graft also underwent necrosis. A re-operation was required, and it was performed with a forearm flap. Patient #3 experienced a fracture of the reconstruction plate 12 months after the primary surgery. A new reconstruction plate was surgically implanted. The same patient had another re-operation 3 years after the primary surgery due to infection of a screw in the plate. 5 years after the primary operation the patient underwent the third re-operation because the fibular graft had fractured. New fibular graft was made using the fibula from the opposite leg. For patient #4 part of the soft tissue portion of the graft underwent necrosis and the bone craft was partially exposed four months after the completion of chemoradiation therapy. A revision surgery was also required which was performed using a local flap. In patient #6 the reconstruction plate protruded through the skin two months after the primary surgery. The defect was initially treated with hyperbaric oxygen therapy but eventually a revision surgery with local flap was required.

Neck dissection was combined in all operations. Two patients had neck dissections also for contralateral side. Nine patients were treated with post-operative chemoradiation and four people post-operative radiotherapy only. The reason why only radiation therapy was used without chemotherapy in these four patients was their poor overall condition, underlying diseases or infection at the surgical side. Radiation therapy was scheduled from five to twelve weeks after the operation. Cisplatin was used in chemotherapy as a chemotherapeutic agent.

All the reconstruction flaps were vital at the time of discharging the patients and at the last postoperative control visit. None of the grafts were lost. 8 out of 13 patients were alive during 5-year follow-up.

Out of the 13 patients in the study, cancer recurred in 8 patients during the 5-year follow-up period. Of these 8 patients, 4 experienced residual tumor, which appeared within 6 months of the completion of radiotherapy and 4 had recurrent tumor, which appeared between 6 months and 5 years after the completion of radiotherapy. One patient, #3, had a second primary tumor, which appeared more than 5 years after the completion of radiotherapy. 4 of the patients experienced local recurrence, while 4 had developed distant metastases. All distant cancers were treated palliatively, and two of the locally recurrent cancers also received palliative treatment. Two locally recurrent tumors and the one local second primary tumor were treated surgically. Patient #2 underwent a local resection, followed by an additional excision due to insufficient margins. The cancer in patient #2 recurred three more times over the following seven years, and ultimately, the cancer could no longer be treated surgically, and chemotherapy was initiated. However, the patient is still alive 10 years after the primary procedure. Patient #3 developed a second primary tumor 62 months after the completion of chemoradiation therapy. This was treated with resection, and a temporal flap reconstruction was performed. However, the cancer recurred after the operation and had metastasized to the neck. Palliative treatment was then initiated. In patient #13, a local early staged squamous cell carcinoma was diagnosed 12 months after the completion of radiotherapy and was successfully treated with a local resection.

Only three patients had osseointegrated dental implants. In patient #2 the implants were placed during the primary surgery, while in patient #3 and #13 implants were placed after the operation and radiation therapy. For patient #2 all four implants remained functional and did not required replacement. In contrast, for patient #3 only one implant remained intact, while three others had to be removed. Two of the implants were placed in the native bone area, and two in the fibula graft bone. The only surviving implant was the anterior one, implanted in the native bone. In patient #13, one implant was already in place before the surgery, and the remaining seven implants were placed after surgery and radiation therapy. The pre-existing implant had to be removed one month after surgery. After the completion of radiation therapy, a total of seven implants were placed, all which remained stable.

Table 1

Patient	Age	Additional diseases	Smoking	Diagnose	Origin	TNM	Gradus
1	66	hypertension	non-smoker	SCC	gingiva	T4aN0M0	II
2	62		former smoker	VC	gingiva	T3N2M0	
3	33		former smoker	SCC	gingiva	T3N1M0	II
4	57		current smoker	SCC	baseos oris	T3N2M0	II
5	71	coronary artery disease	non-smoker	SCC	gingiva	T4aN0M0	I
6	67	psoriatic arthitis	former smoker	SCC	gingiva	T4aN1M0	II

7	76	hypertension	former smoker	SCC	retromolaris	T4aN1M0	II
8	66	hypertension	current smoker	SCC	gingiva	T4aN2M0	I
9	76	atrial fibrillation, hypertension, arteriosclerosis obliterans	former smoker	SCC	baseos oris	T4aN0M0	I
10	69	hypertension, osteoporosis	non-smoker	SCC	retromolaris	T4aN2M0	
11	60	hypertension	current smoker	SCC	buccae	T4aN0M0	II
12	82	hypercholesterolemia, arthrosis, osteoporosis	non-smoker	SCC	gingiva	T4aN0M0	
13	74	hypertension, hyperholesterolemia, esophagitis	non-smoker	SCC	gingiva	T4aN2M0	II

SCC = squamous cell carsinoma
VC = verrucous carsinoma

Table 2

Patient	Flap	Radiation/ chemoradiation	Neck dissection	Implants	Lost implants
1	fibula	CRT	ipsi	-	
2	fibula	CRT	ipsi	4 in primary operation	0
3	fibula	CRT	ipsi	4 after primary operation	3
4	fibula	CRT	ipsi+contra	-	
5	fibula	CRT	ipsi+contra	-	
6	fibula	CRT	ipsi	-	
7	fibula	CRT	ipsi	-	
8	fibula	CRT	ipsi	-	
9	fibula	CRT	ipsi	-	
10	fibula	RT	ipsi	-	
11	fibula	RT	ipsi	-	
12	fibula	RT	ipsi	-	
13	fibula	RT	ipsi	1 earlier installed, 7 after primary operation	1

CRT = chemoradiation therapy
RT = radiation therapy

Table 3

Patient	Status of the flap	Margins	Residual/ recurrent tumor	First recurrent (months)	Residual type	Treatment	5-year status
1	Vital	grows to margin	yes	3	distant metastases	palliative	dead
2	Vital	sufficient margin	yes	10	local	operation	alive
3	Vital	close margin	no				alive
4	Vital	close margin	yes	10	distant metastases	palliative	dead
5	Vital	close margin	yes	3	local	palliative	dead
6	Vital	sufficient margin	no				alive
7	Vital	sufficient margin	no				alive
8	Vital	grows to margin	no				alive
9	Vital	grows to margin	yes	0	distant metastases	palliative	alive
10	Vital	close to margin	yes	3	local	palliative	alive
11	Vital	sufficient margin	yes	22	distant metastases	palliative	dead
12	Vital	sufficient margin	no				dead
13	Vital	grows to margin	yes	12	local	operation	alive

grows to margin 0 mm
close margin from 0,01mm to 4 mm
sufficient margin over 4 mm
first recurrent counted in months from the completion of radiotherapy

Discussion

After segmental mandibulectomy, there are significant challenges regarding the esthetic and functional outcomes of the patient`s jaw. Surgical results in these aspects have improved considerably with the introduction of microvascular flaps. Fibular flap is the preferred flap for mandibular reconstruction due to its low failure rate. (2) In the management of advanced head and neck cancers, a combination of surgery and radiation therapy has been shown to offer significant benefits. However, the success of microvascular flaps in combined with radiation therapy remains a topic of debate, with outcomes thought to be influenced by both timing and radiation dose. (4) (5)

Radiation therapy also affects the surrounding healthy tissues, leading to fibrosis and a reduction in capillary formation, which can lead to problems in the tissue bed and wound healing. Therefore, postoperative radiotherapy is initiated only after the surgical wound has completely healed, and the microvascular flap has successfully integrated into the surrounding tissues.

In this study, all 13 grafts remained viable. The results for the microvascular flaps were favorable, and based on this study, radiation therapy did not appear to affect bone graft survival. However, there were complications related to the soft tissue of the grafts in several cases, most of which became apparent only after the initiation of radiation therapy. Five patients experienced necrosis or fistulization of the soft tissue portion of the graft, and four of them required reoperation.

Our results were consistent with a previous study by Irjala et al. (3) They analyzed the surgical outcomes of 10 patients who underwent segmental mandibulectomy and vascularized fibula reconstruction with preoperative radiation therapy at Turku University Hospital. The surgery was scheduled within 5 weeks of radiation therapy. The results were nearly as favorable regarding graft survival, with only one microvascular graft lost. In their study it was anticipated that postoperative radiation therapy would negatively affect the graft and increase graft loss, but this did not appear to be the case based on our current study. Regarding the incidence of complications, studies have yielded conflicting results. In the study by Choi et al., the impact of radiation therapy on complication incidence in patients who underwent fibular flap reconstruction due to cancer or benign disease was compared. The study involved 100 patients, who were divided into three groups based on their radiation therapy treatment: 1) no RT, 2) preoperative RT and 3) postoperative RT. The results indicated no significant difference in the occurrence of complications between the groups. (6) Similarly, in the study by Deutsch et al., no significant difference was found between preoperative and postoperative radiation therapy regarding to complication rates. (7) In contrast, Shaw et al. concluded in their study that postoperative radiotherapy was strongly associated with complications, particularly in plate fixation and soft tissue complications. (8)

Despite the successful viability of all flaps, cancer recurrence posed a significant challenge, with 8 out of 13 patients experiencing recurrence within the 5-year-follow-up period. The highest recurrence risk occurred within the first 2 years post-surgery. This is consistent with previous studies on head and neck cancers. The incidence of recurrent HNC tumor is highest within the first 2 years, with most recurrences occurring within 3 years after treatment. (9) The recurrence rate was surprisingly high in this study, 62%, which is higher than what is reported in the literature. Factors that increase the risk of cancer recurrence include a positive or close surgical margin, as well as a high-grade cancer. In this study, among the 13 patients, 4 had cancer growth at the edge of the specimen, and 4 had insufficient margins (ranging from 0,01 mm to 4 mm). Recurrence of cancer was observed in 6 of these patients during follow-up. Insufficient margins significantly increase the risk of cancer recurrence.
In such cases the adjuvant therapies can play a crucial role in improving the patient`s prognosis and preventing disease recurrence, as observed in patient #8 in this cohort. Patient #8 had a positive surgical margin, but with the postoperative chemoradiation therapy the cancer was effectively treated and did not recur during follow-up. Patient #8 is still alive.

Surgical management of head and neck cancers is always balancing between achieving sufficient surgical margins and minimizing the morbidity associated with tissue defects. In certain situations, obtaining the recommended margins may not be feasible without significantly impairing the patient`s quality of life. Beyond aesthetic considerations, a successful reconstruction also facilitates essential functions such as speaking and mastication. Dental implants are used to improve the aesthetic and functional outcomes after mandibular reconstruction, which has a significant impact

on the quality of life for patients. Dental implants belong to rehabilitations in patients who are free of disease, motivated and in good condition and the bony structure allows implant placement. Studies have shown that irradiation of the fibula flap negatively affects the survival of implants. Implants also tend to perform worse when attached to the fibula graft compared to those anchored to the native bone. (10) (11) In our study, three patients received dental implants, and only one patient had all the implants survive completely. In patient #2, all four implants placed during mandibular reconstruction surgery survived. In patient #3, four implants were placed after radiation therapy, and of these, only the one implanted on the native bone side survived, while the others were lost. Patient #13 had one implant already in place before surgery, which had to be removed after surgery due to its poor prognosis. However, the other seven implants of patient #13, which were placed after radiation therapy and anchored to the native bone, remained stable. The results of our study regarding implants are consistent with other studies, such as those by Tahmasebi at al. (10), Ch`ng et al. (11) and Pellegrino et al. (12) The implants that were implanted to the native bone remained more stable than those attached to the fibula graft. Our study also suggest that implants placed directly during the surgery, before radiation therapy, had a higher survival rate compared to those implanted later into bone that had already been irradiated. However, due to small number of implants in our study sample, no further conclusions can be drawn, and more studies are needed to confirm this observation.

The major limitation of this study is its small sample size with only 13 patients. This limits the generalizability of the results and affects the scope of conclusions that can be drawn from this study. Additionally, the heterogeneity of the patient population, including age, smoking history, and comorbidities, may have influenced the results. Smoking and other health conditions are important factors that may affect wound healing and tolerance of radiotherapy. A strength of our study is that it includes a comparison with data from the same clinic, involving patients who were treated differently, namely with preoperative radiation therapy, while the rest of the treatment protocol remained the same.

In conclusion, postoperative radiotherapy can be successfully combined with microvascular fibular reconstruction surgery, when combined therapy is needed for an advanced stage oral cancer. Flap viability remains good when radiotherapy is initiated after a proper healing process. In this study, none of the fibula grafts were lost. However, postoperative radiotherapy may contribute to an increased risk of soft tissue complications of the flap. In terms of dental implants, it seems that radiation therapy has a negative impact on implant survival, particularly when the implants are placed in the fibular graft bone. However, the sample size for implants in our study was very small. Regarding cancer recurrence, the result in our study was surprising, and compared to the previous study by Irjala et al. (3), the recurrence rate was significantly higher, with 62% of cancers recurring during follow-up, whereas Irjala et al. reported a recurrence rate of 20%.

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