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DYNC1H1, and *TP53* genes were predicted as potentially pathogenic according to several predicted algorithms (SIFT, PolyPhen2, MutationTaster, or LRT) (Table 1). It should be noted that in this sample, we did not find any germline mutations in known genes associated with paragangliomas (*VHL, SDHA, SDHB, SDHC, SDHD, NF1, RET, HRAS, KRAS, EPAS1 (HIF2A), ATRX, CSDE1, BRAF, FGFR1, FGFR2, FGFR3, FGFR4, FGFRL1, SETD2, ARNT, TP53, TP53BP1, TP53BP2, TP53I13, KMT2D, BAP1, IDH1, IDH2, SDHAF1, SDHAP2, FH, EGLN1, MDH2, TMEM127, MAX, KIF1B, MEN1, GDNF, GNAS, CDKN2A, BRCA1*, and *BRCA2*).

Table 1

Potentially pathogenic somatic mutations in the sample with the highest ML.

Gene	dbSNP ID	GenBank	Coordinate	Nucleotide change	Amino acid change	Genotype
PRDM2	rs756985448	NM_012231.4	chr1: 14,106,977	c.2687A>G	p.Tyr896Cys	Het
ASPM	-	NM_018136.4	chr1: 197,097,759	c.2797T>A	p.Phe933Ile	Het
OSBPL11	-	NM_022776.4	chr3: 125,2863,04	c.802T>G	p.Leu268Val	Het
PCOLCE2	-	NM_013363.3	chr3: 142,542,410	c.913G>A	p.Gly305Arg	Het
ZFAND5	-	NM_001102420.2	chr9: 74,970,993	c.518T>G	p.Leu173Trp	Het
NEK3	-	NM_002498.2	chr13: 52,722,548	c.603+2T>G	-	Het
DYNC1H1	-	NM_001376.4	chr14: 102,469,248	c.4829A>G	p.Lys1610Arg	Het
TP53	rs587781525	NM_000546.5	chr17: 7,577,096	c.842A>T	p.Asp281Val	Het

Six of eight potentially pathogenic somatic variants in *ASPM, OSBPL11, PCOLCE2, ZFAND5, NEK3*, and *DYNC1H1* genes have been previously described neither in databases nor in literature. The mutation NM_012231.4: c.2687A>G, p.Tyr896Cys (chr1: 14,106,977, rs756985448) in *PRDM2* was annotated in dbSNP with uncertain clinical effect. According to gnomAD database it is more likely non-pathogenic variant. The mutation NM_000546.5: c.842A>T, p.Asp281Val (chr17: 7,577,096, rs587781525) in *TP53* gene was described in dbSNP both as a germline and somatic mutation, and has a pathogenic clinical significance according to the ClinVar database.

Conclusion

Our results report several potentially pathogenic somatic mutations that can be involved in CBT pathogenesis.

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RECONSTRUCTIVE SURGERY FOR ORAL CAVITY CANCER

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Introduction. Treatment of patients with advanced oral cavity cancer remains challenging. **Material and Methods.** We analyzed 127 reconstructive operations performed in patients with oral cancer. We used free (90 cases - 71%) and pedicle (37 cases - 29%) flaps for the reconstruction**. Results.** Good functional results were achieved in most cases (85%). Adequate mobility of the tongue was restored by using skin-fascial flaps. In cases with maxillofacial reconstruction, the mandibular and maxillary continuity, natural facial contour and mouth opening were restored using bone flaps. **Conclusions.** To achieve good functional and cosmetic results, as well as to reduce postoperative complications of reconstructive surgery in patients with oral cavity tumors, an adequate reconstructive material should be selected.

Keywords: oral cavity cancer, reconstructive surgery, microsurgical reconstruction.

Introduction

In Russia, there has been a steady increase in the incidence of oral cancer. In the period from 2006 to 2016, the overall rise in the incidence of oral cancer was 29.93% for men and 54.61% for women [1]. Surgery is the main treatment for oral cancer, often requiring resection of the tongue, mandible, palate, oral/buccal mucosa, lip and the skin of the chin. Reconstructive surgery following extensive resections is an important aspect in the treatment of patients with oral cavity tumors [2]. Microsurgical reconstruction techniques allow the indications for radical surgical resections to be expended [3, 4]. However, the use of pedicle flaps in reconstructive surgery of the oral cavity has not lost its relevance. Management of patients with locally advanced oral cavity cancer, especially reconstructive surgery, remains a challenge [3, 5].

Material and Methods

Between 2008 and 2017, 115 patients with oral cancer were treated at the Department of Head and Neck Tumors of the Cancer Research Institute (Tomsk, Russia). All patients underwent surgical resection with reconstruction. A total of 127 reconstructive surgeries were performed (12 patients underwent two reconstructions). The distribution of patients according to the clinical stage was as follows: 16 patients with stage T2, 62 with T3, and 37 with T4. According to the presence of regional metastases in neck lymph nodes, there were 19 patients with N1 and 8 patients with N2. There were 44 women and 71 men. Primary cancer was detected in 63 cases (55%) and recurrent cancer in 52 cases (45%).

Distribution of tumor localization was as follows: tongue in 37 cases (32%), alveolar mucosa of the mandible in 24 (21%), mucosa of the mouth floor in 19 (17%), mucous cheeks in 14 (12 %), alveolar mucosa of the maxillary in 14 (12%), upper and lower lip in 7 cases.

In 90 cases (71%), free flaps were used as a reconstructive material: fibula flap in 40; ALT flap in 24; radial free flap in 12; medial sure artery perforator flap in 5; thoracodorsal flap in 4; osteocutaneous scapula free flap in 3; great omentum flap in 1; iliac crest free flap in 1. We used also pedicle flaps (37 cases): pectoral major myocutaneus flap in 17 cases and submental flap in 20 cases.

It should be noted that free flaps were mostly used to close large, composite (bone-soft-tissue) defects. Pedicle flaps (mostly submandibular flap) were used to reconstruct small defects of the tongue (hemigloselectomy), mucosa cheeks (up to 7×7 cm), or in a case of extensive defects in the tongue and oral cavity in patients with an unfavorable prognosis (pectoral flap).

Results

In most cases (85%), good functional results were achieved. In cases of tongue reconstruction using skin-fascial flaps, adequate mobility of the tongue was restored. Tongue reconstruction with skin-fascia flaps provided adequate tongue mobility and favorably influenced the speech and nutrition rehabilitation. Defects of the 1/2 tongue were reconstructed using free flaps (radial, medial sure artery perforator flap or ALT flap), or by pedicel flaps (submental flap). The ALT flap or pectoral major myocutaneus flap was used to reconstruct total defects of the tongue. It should be noted that the length of surgery was much less using a pedicle flap than a free flap (214.1 versus 580.88 minutes). In cases with reconstruction of *maxillary* and *mandibular* bone defects with *autotransplantation* and *bone* grafting, a successful restoration of the continuity of mandible and maxilla, natural contour of the face and mouth opening was achieved. The use of chimeric fibular flaps allowed restoration of extensive defects of the oral cavity, soft tissues of the buccal region and the mandible. The average length of a hospital stay following reconstructive surgery did not exceed 21 days (usually 14-18 days).

Flap necrosis was observed in 15 cases (12%). Necrosis of the fibula flap due to the formation of the saliva flowing to the area of microvascular anastomoses was the most common (10 cases,

8%). Partial necrosis of the flaps was noted in 5 cases (4%). Recurrences occurred in 25 cases (22%): local recurrence in 18 cases (16%) and neck lymph node metastases in 7 cases (6%). Distant metastases were observed in 2 cases (brain and skull bones).

Conclusion

Reconstructive surgery following radical surgical resection for oral cavity cancer contributes to the improvement of survival outcomes and social adaptation of the patients. To obtain good functional and cosmetic results, as well as to reduce postoperative complications, an apropriate reconstructive material should be selected. This choice should be based on the assessment of tumor involvement, reconstructive surgery extent and previous treatment.

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LOW COUNT OF LYMPHOCYTES AND CD4T-CELLS IN PERIPHERAL BLOOD OF PATIENTS WITH PRIMARY HODGKIN'S LYMPHOMA CORRELATES WITH UNFAVOURABLE DISEASE PROGNOSIS

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The prognostic significance of depletion of lymphocytes and of CD4T-cells was assessed in a retrospective cohort study of 162 Hodgkin lymphoma (HL) patients. The moderate CD4 lymphopenia (400-210 μL) was observed in all subgroups. The deep CD4 lymphopenia (≤200 μL) was found in 15% patients; it was associated with age ≥45 (p=0.031), advanced stage (p=0.03) and IPS score ≥4 (p=0.000). Overall survival (OS) and progression-free survival (PFS) for all 162 patients correlated with baseline CD4T-cells counts. At a median follow up of 60 months, all patients with CD4T-cells count ≤400 μL had lower progression-free survival (PFS) and lower overall survival (OS) compared with those without CD4 lymphopenia. In I-II favorable stages (n=13), progression occurred only in 1 patient with low CD4 count; OS was 100%. In I-II unfavourable stages (n=29), 6 patients with CD4 deficiency had PFS 50% vs. 95% in the rest, p=0.007; OS was 30% vs. 100%, p=0.001. Among 120 patients with stages III-IV, those with low CD4 count (n=53) had 5-year PFS 64% compared with 87% in patients without CD4 deficiency, p=0.006. Overall survival in advanced HL with low CD4 count was 70%, compared with 95%, p=0.004. Subset analysis in 94 patients with stages III-IV plus IPS 0-3 supported negative impact of CD4 lymphopenia. PFS in «low CD4» patients was 69% vs. 88%, p=0.054; OS was 76% vs. 97%, p=0.058.

Keywords: lymphocytes count, CD4T-cells, Hodgkin lymphoma, unfavourable prognosis.

Introduction

Initial pre-treatment lymphopenia (PL) is associated with negative prognosis in different malignancies, including lymphomas [1]. CD4 deficiency is known to accompany the impaired immunity in classical HL and has been recently shown to play a negative role in various solid tumors and Non-Hodgkin's lymphomas [2-4]. As part of reactive microenvironment, CD4T-cells play a key role in tumor-response regulation the activation of effector-cells. However, during progression the tumor acquires certain features that allow it to avoid immunological surveillance [5].

In a retrospective cohort study, long term relapse-free survival and overall survival were assessed in 162 HL patients with depletion of lymphocytes and CD4T-cells.