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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
<i>PRDM2</i>	rs756985448	NM_012231.4	chr1: 14,106,977	c.2687A>G	p.Tyr896Cys	Het
<i>ASPM</i>	-	NM_018136.4	chr1: 197,097,759	c.2797T>A	p.Phe933Ile	Het
<i>OSBPL11</i>	-	NM_022776.4	chr3: 125,2863,04	c.802T>G	p.Leu268Val	Het
<i>PCOLCE2</i>	-	NM_013363.3	chr3: 142,542,410	c.913G>A	p.Gly305Arg	Het
<i>ZFAND5</i>	-	NM_001102420.2	chr9: 74,970,993	c.518T>G	p.Leu173Trp	Het
<i>NEK3</i>	-	NM_002498.2	chr13: 52,722,548	c.603+2T>G	-	Het
<i>DYNC1H1</i>	-	NM_001376.4	chr14: 102,469,248	c.4829A>G	p.Lys1610Arg	Het
<i>TP53</i>	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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REFERENCES

1. Zhikrivetskaya S.O., Snezhkina A.V., Zaretsky A.R., Alekseev B.Y., Pokrovsky A.V., Golovyuk A.L., Melnikova N.V., Stepanov O.A., Kalinin D.V., Moskalev A.A., Krasnov G.S., Dmitriev A.A., Kudryavtseva A.V. Molecular markers of paragangliomas/pheochromocytomas. *Oncotarget*. 2017 Apr 11; 8(15): 2575625782. doi: 10.18632/oncotarget.15201.
2. Kiseleva M.V., Abakushina E.V., Tsyb A.F. Reproductive health of cancer patients: the state of the problem. *Journal of N.N. Blokhin Russian Cancer Research Center RAMS*. 2009; 20(2): 66. [in Russian]
3. Kiseleva M.V., Karpeikina M.M., Komarova E.V., Malinova I.V., Denisov M.S., Chudakov K.V. The ability to restore ovarian function in cancer patients. *Journal of N. N. Blokhin Russian Cancer Research Center RAMS*. 2013; 24(34): 4345. [in Russian]
4. Kiseleva M.V., Komarova E.V., Malinova I.V., Karpeikina M.M., Denisov M.S. Recovery of fertility in cancer patients by the method of retransplantation of vitrified ovarian tissue. *Reproductive medicine. Scientific and practical journal*. 2013b; 16(34): 3335. [in Russian]
5. Snezhkina A.V., Lukyanova E.N., Kalinin D.V., Pokrovsky A.V., Dmitriev A.A., Koroban N.V., Pudova E.A., Fedorova M.S., Volchenko N.N., Stepanov O.A., Zhevelyuk E.A., Kharitonov S.L., Lipatova A.V., Abramov I.S., Golovyuk A.V., Yegorov Y.E., Vishnyakova K.S., Moskalev A.A., Krasnov G.S., Melnikova N.V., Shcherbo D.S., Kiseleva M.V., Kaprin A.D., Alekseev B.Y., Zaretsky A.R., Kudryavtseva A.V. Exome analysis of carotid body tumor. *BMC medical genomics*. 2018 Feb 13; 11(Suppl 1): 17. doi: 10.1186/s12920-018-0327-0.

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 expanded [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 myocutaneous 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 (hemiglossectomy), 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 pedicle flaps (submental flap). The ALT flap or pectoral major myocutaneous 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 appropriate 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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REFERENCES

1. Caprin A.D., Starinsky V.V., Petrova G.V. The state of oncological care for the population of Russia in 2016. Moscow: MNI OI P.A. Gertsena is a branch of the National Medical Research Radiological Centre of the Ministry of Health of Russia, 2017. 236.
2. Shah J.P., Patel S.G. Head and neck surgery and oncology. Mosby; 2013. 713.
3. Kulbakin D.E., Chonzonov E.L., Mukhamedov M.R., Garbukov E.U., Shtin V.I., Havkin N.M., Vasilev R.V. Reconstructive plastic surgery in combined treatment of patients with locally advanced head and neck tumors. Questions of oncology. 2017; 63 (6): 862-6.
4. Hanasono M.M. Reconstructive Surgery for Head and Neck Cancer Patients. Adv Med. 2014; 2014: 795483. doi: 10.1155/2014/795483.
5. Neligan P.C. Head and Neck Reconstruction. Plastic and Reconstructive Surgery. 2013; 131: 260-9

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 μ L) was observed in all subgroups. The deep CD4 lymphopenia (\leq 200 μ L) was found in 15% patients; it was associated with age \geq 45 ($p=0.031$), advanced stage ($p=0.03$) and IPS score \geq 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 \leq 400 μ L 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.