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*Retrospective Study*

**Recurrent oropharyngeal cancer: Analysis of surgical treatment outcomes**

TLRM for Recurrent oropharyngeal cancer.

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### **Abstract**

#### BACKGROUND

**Background:** This study aimed to introduce transoral robotic surgery and laser resection (TLR) as a considerable way of treatment patients with recurrent oropharyngeal malignancies.

#### AIM

**The aim of the study** is the development of a foundation for minimally invasive transoral surgical technique for patients with oropharyngeal recurrence process

#### METHODS

**Methods:** This study prospectively and retrospectively included patients with recurrent tumors from 2003 to 2018. Subjects were allocated into two groups: (1) Group I; underwent TRL; (2) Group II (control) underwent open surgeries of varying volume. Evaluation was done with intraoperative blood loss count, postoperative infection incidence, and quality of life using the scale for patients with head and neck tumors FACT&N.

## RESULTS

**Results:** 141 patients were included (103 males and 38 females), in 82 cases (85.4%), a recurrent tumor developed earlier than a year after primary tumor therapy; 46 were in Group I and 69 in Group II, age ranging from 18 to 86 years (average: 57.6 years). First group showed a statistically significant less amount of blood loss and decreased incidence of infectious complications ( $P < 0.05$ ). Additionally, there was a significant difference in functional outcomes (quality of life scores) but no significant difference in survival curves.

## CONCLUSION

**Conclusions:** In properly elected patients TLR is not just reasonable but tends to be a favorable alternative for recurrent oropharyngeal cancer compared to the outcomes of open surgery group.

**Key Words:** Key words: Oropharyngeal cancer; transoral laser resection; open surgery; recurrent tumor; oropharyngeal squamous cell carcinoma

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**Core Tip:** Our study included a large retrospective part and two prospective compare groups of patients, who were subjected to open surgery or TLR. The results show that in properly elected patients TLR is not just reasonable but has a tendency to be a favorable alternative for recurrent oropharyngeal cancer compared to the outcomes of open surgery group. TLR in our study was associated with shorter operating time, lower blood loss counts and postoperative complications rate, higher quality of life and proportionate 2-year survival when compared with open surgery performance rates. As

open surgery was for decades the mainstream treatment approach for recurrent tumors of the oropharyngeal zone considerable experience is accumulated, which indicates that this management bears unfavorable functional outcomes. The results of our comparative study defined higher quality of life in patients who underwent TLR.

## **INTRODUCTION**

### **Introduction**

Malignant tumors of the oral cavity and oropharynx compose around 2-5% of all malignancies. The current mainstream of first-line treatment for oropharyngeal squamous cell carcinoma (SCC) is function preserving chemoradiation. After neoadjuvant chemoradiotherapy salvage surgery for local recurrent tumor is widely deemed as the only possible treatment strategy that may establish curative effect. The possibilities of life-saving operations in such cases are limited by the complexity of surgical access, high probability of serious complications, proximity to vital organs and structures, and the general health of patients during relapse. Unfortunately, salvage interventions which incorporate open surgical access in the head and neck region are associated with prolonged hospital stay, high intraoperative blood loss counts, decreased survival prognosis, and quality of life. These interventions also may require additional bone resection and/or reconstructive component, which incorporate regional pedicle flap or a microsurgical flap.

Recently evolving transoral robotic surgery and transoral laser microsurgical resection (TLMR) have a potential to overcome the morbidities associated with open surgery. Published academic data suggests that a considerable fraction of subjects with recurrent oropharyngeal cancers may benefit from performance of TLMR. Currently very limited data is available on comparison of surgical, oncologic and functional results in patients with recurrent oropharyngeal SCC treated with TLMR with those treated with traditional open surgical approaches. The purpose of the study was to compare surgical, functional and oncologic outcomes in patients undergoing open

surgery *vs* TLMR, and to determine the role of minimally invasive surgical techniques in management of recurrent oropharyngeal tumors.

## MATERIALS AND METHODS

**All study participants provided informed written consent prior to study enrollment for the surgical procedure.**

According to the medical archive, from 2003 to 2018, 141 patients with recurrent oropharyngeal tumors were observed at the N.N. Blokhin National Research Center of Oncology (BNRCO). The clinical data of the patients were analyzed retrospectively and prospectively.

The following clinical parameters were evaluated in all patients: Gender, age at the time of diagnosis, localization of the primary tumor, method of treatment of the primary tumor, morphological properties of the primary tumor, presence of adjuvant therapy, date of the first progression after treatment of the primary tumor, localization of metastases, systemic chemotherapy for recurrence of the primary tumor and realized metastases, both regional and long-term, overall survival and progression-free survival (PFS) on the background of treatment. The date of death and disease progression was estimated according to the data provided by the out-patient monitoring department. The date of the visit was established by analyzing outpatient records of the patient's visit to the out-patient department of BNRCO.

To conduct a comparative analysis of the effectiveness of TLMR compared to salvage surgery, a comparison group was identified and included 25 patients. To assess operative outcomes intraoperative blood loss counts, and postoperative infection incidence were compared between the two study groups. Functional results were evaluated by comparative assessment of the quality of life by the Functional Assessment of Cancer Therapy-Head & Neck Scale (FACT&N) in the groups of TLMR and open surgery.

**Statistics ( was performed by MicrosoftExcel 2022, SPSS 22 StatSoft Inc).**

Life expectancy and time to progression were evaluated using the Kaplan-Mayer method and compared by a log-rank test. Chi-squared tests and Fisher's exact criterion were used to verify the validity of differences in the values of features in the groups. The differences were considered statistically significant at  $P < 0.05$ . The correlation was carried out using the Pearson correlation coefficient and Spearman's rank correlation coefficient. The Cox proportional regression analysis model was used to assess the independence of traits and calculate comparative risk (CR).

## **RESULTS**

### Patient population

The study included 141 patients who underwent treatment at BRNCO and underwent surgery for recurrent oropharyngeal tumors. 21 (14.9%) patients received primary treatment at our institution and 120 (85.1%) patients were treated in other medical institutions. Of the examined patients, 38 (27.0%) were women, 103 (73.0%) were men. The mean age of the enrolled patients was 57.6 [52.0; 66.5] years, minimum 18, maximum 86 years

## **DISCUSSION**

Chemoradiotherapy as the initial function preserving treatment mode for oropharyngeal cancers has shown good effect nevertheless up to one third of cases demonstrate locoregional relapses. Until recently, the only way to treat such cases was open access surgery. However, oncologic results of such interventions are modest. Five-year survival rate was reported to range between 26% and 49.1% for patients who underwent salvage surgery.<sup>1,2</sup>

Advancements in endoscopic surgery have led to the development of minimally invasive techniques that enable transoral surgery as an alternative to transmandibular and or transcervical approaches. TLRM was the first minimally invasive technique to be applied to oropharynx. High-volume TLRM surgeons have reported favorable oncologic outcomes using TLRM in case for oropharyngeal recurrence . However, the

technical challenges of this method have limited widespread adoption outside of select large academic centers. The target of a transoral approach is different in patients with recurrent tumors of the oropharynx. In these cases, surgery may be the only available means of treatment or a method for treatment intensification. Small-volume recurrent can be manageable to a transoral approach without reconstruction. Hence considering the effect of prior radiation on wound healing and the risk of life threatening complications (bleeding) after transoral surgery, large-volume recurrent oropharyngeal tumor may require simultaneous microvascular reconstruction.

Our study included a large retrospective part and two prospective compare groups of patients, who were subjected to open surgery or TLRM. The results show that in properly elected patients TLRM is not just reasonable but has a tendency to be a favorable alternative for recurrent oropharyngeal cancer compared to the outcomes of open surgery group. TLRM in our study was associated with shorter operating time, lower blood loss counts and postoperative complications rate, higher quality of life and proportionate 2-year survival when compared with open surgery performance rates. As open surgery was for decades the mainstream treatment approach for recurrent tumors of the oropharyngeal zone considerable experience is accumulated, which indicates that this management bears unfavorable functional outcomes. The results of our comparative study defined higher quality of life in patients who underwent TLRM.

Postoperative surgical complications are observed occasionally after salvage open surgery of recurrent oropharyngeal cancer, these may include infectious complications as well as wound healing problems. This was supported by our observations. The complication rate seen in the TLMR group was lower than for open surgery. Such parameters as blood loss counts, operative time and occurrence of postoperative infectious complications were all lower in the TLRM study group. Considerations that are to be taken in account when planning TLRM as treatment for recurrent oropharyngeal cancers are: The size and exact location of the lesion and personal operator's experience with this technique.



Surgical treatment alone or in combined approaches are main methods of choice for the treatment of recurrent tumors, if surgery is possible to perform. Many authors pointed better survival rates in surgical treatment of relapses compared to those in conservative treatment.

B.S. Koo *et al* (2006) analyzed the effectiveness of treatment in 23 patients with recurrent oral cancer. Of these, 13 underwent surgery, 10 - chemotherapy or radiation therapy. The median overall survival in patients who have been undergoing surgical treatment significantly exceeded that in conservative treatment.<sup>3</sup>

M.E. Zafereo *et al.* (2009) note that the three-year overall survival for patients who underwent salvage surgery, reradiation therapy, palliative chemotherapy, or replacement therapy was 48.7%, 31.6%, 3.7%, and 5.1%, respectively.<sup>4-9</sup>

According to K.S. Choe *et al.* (2011), two-year survival rates in patients treated with chemoradiotherapy alone were significantly lower compared to those in patients undergoing salvage surgery (10.8% and 28.4%, respectively). The authors conclude that, due to the high risk of severe toxicity, repeated chemoradiotherapy should be performed only in a strictly selected group of patients.<sup>10-14</sup>

S. Kano *et al.* (2013), in an analysis of 11 patients who underwent salvage surgery and 24 who underwent conservative treatment, showed statistically significant differences in five-year survival (49.1% and 16.3%, respectively).<sup>1</sup>

M.A. Kropotov *et al.* (2016) points out that due to the emergence of new effective techniques for the surgical treatment of patients with oropharyngeal cancer, the chemoradiation approach is no longer considered as the method of choice in the treatment of such patients. However, further randomized trials are needed to individualize the treatment approach and choose the optimal treatment tactics for a particular patient.<sup>15-17</sup> The specific medical literature sources possess a considerable number of studies describing the effectiveness of surgical treatment of primary oropharyngeal cancer. Little attention is paid to the exploring process of therapy of the relapse tumor. In addition, as noted by S.C. Jayaram *et al.* (2016), the quality of many studies could not be considered good enough<sup>18-22</sup>: all studies were retrospective, some



had an extremely small sample size (29 patients,<sup>23-27</sup> 39 patients<sup>28-30</sup>). The greatest hindrance to an adequate assessment is caused by the heterogeneity of the groups and the lack of adjustment of the result to possible predictors of effectiveness. Thus, the association of a tumor with the human papillomavirus was considered only in one clinical study.<sup>31</sup> A.J. Kim (2007) reported that 74% of patients had a second relapse on average 9 months after salvage surgery,<sup>32-34</sup> according to M.E. Zafereo *et al.* (2009) the recurrence rate was 66%, the onset time was 8 months on average.<sup>35,36</sup>

S.C. Jayaram *et al.*, based on meta-analysis of recurrent oropharyngeal malignancies treatment showed the mean effect value for three-year overall survival to be 26% with moderate heterogeneity (I<sup>2</sup> = 40.7%), the mean effect value for five-year overall survival was 23%, with high heterogeneity (I<sup>2</sup> = 73.9%).<sup>37,38</sup> However, it should be noted that this meta-analysis is based on studies conducted during the period 1976-2014, and the above indicators describe the effectiveness of rescue operations over the entire period.

At the same time, the authors indicate that there was a significant positive trend in 5-year survival over this period: 20% for studies conducted before 2000 and 35% after 2000 ( $P < 0.001$ ). Such a phenomenon may be associated both with an improvement in the technique of surgical intervention, an increase in the quality of the algorithm for assessing the possibility of surgical treatment, and an increase in the relative frequency of tumors associated with the human papillomavirus.

This literature review considers the results of studies conducted in 2006-2016. A.C. Nichols *et al.* (2011), considering the effectiveness of salvage operations in 29 patients with recurrent oropharyngeal cancer, determined two-year survival rates of 64.5%, five-year survival rates of 43.4%.<sup>39</sup>

C. Fakhry *et al.* (2014) conducted a comparative analysis of the effectiveness of surgical treatment of recurrent oropharyngeal cancer in patients associated (49 patients) and non-associated (29 patients) with human papillomavirus. The overall two-year survival rate for p16-positive patients was 72%, for p16-negative patients it was 45% ( $P = 0.004$ ).<sup>40</sup>

## **CONCLUSION**

In conclusion, we would like to point it out that despite the impressive success of surgery as the best way of treatment patients with oropharyngeal recurrent tumors, we strictly assume that this cohort of patients should be carefully stratified managed and thoroughly discussed with multidisciplinary team of specialists before surgery.

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