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# The management of oral cancer – current standards and future perspectives. Review of the literature

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**The management of oral cancer – current standards and future perspectives. Review of the literature**

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Oral cancer (OC) is one of the most common cancers of the head and neck region, with approximately 1,950 new cases reported in Poland in 2019. The main factors contributing to the development of OC are cigarette smoking and excessive alcohol consumption. Squamous cell carcinoma accounts for more than 90% of all OCs. In patients with OC surgery is the treatment of choice, but there is a high number of patients who require complementary treatment – radiotherapy or radiochemotherapy. The treatment of these tumours should be comprehensive and multidisciplinary. Due to suboptimal treatment outcomes in this patient group, numerous clinical trials are being conducted to search for new, more effective treatments. The aim of this study was to review the literature on current and new methods of diagnosis and treatment of OC and to analyse the clinical trials currently available for OC patients in Poland. Despite the use of modern drugs, only modest progress has been made in terms of treatment efficacy.

**Key words:** oral cancer treatment, clinical trials

## Introduction

Oral cancer (OC) is one of the most common cancers in the head and neck region. In 2020, there were 377,713 new cases worldwide, with the highest incidence found in the Asian countries of Pakistan, Sri Lanka and India [1]. According to the American Joint Committee on Cancer (AJCC) classification, OC is

a squamous cell carcinoma (SCC) originating in the mucosa of the upper and lower lip, cheek, retromolar trigone, vestibule of oral cavity, alveolar process and upper and lower gingiva, hard palate, movable part of the tongue and floor of the mouth. Treatment of tumors located in this area should be comprehensive and multidisciplinary. The aim of this study was to review the literature on current and new methods for diagnosing and treating oral cancer and to analyse the clinical trials currently available for oral cancer patients in Poland.

**Epidemiology**

Epidemiological data show that in 2019, approximately 1,950 new cases (accounting for approximately 1.13% of all malignancies) and 1,234 deaths from OC were reported in Poland [2]. According to World Health Organisation (WHO) data, Poland ranked 5th in Europe in the number of new cases (after Ukraine, Belarus, Hungary and Latvia) and 6th in Europe in the number of deaths (after Ukraine, Romania, Lithuania, Malta and Moldova) due to OC [1-2]. According to a report by the National Cancer Registry, since 2001, there has been a clear upwards trend in both incidence and mortality from OC for all possible locations except for lip cancer in men, where there has been a gradual decline in incidence. Men are more frequently affected by OC. The movable part of the tongue (data for 2019) is the most common oral location of OC in the Polish population at present. The peak incidence of OC occurs after the age of 50 years [1].

**Ethiology**

The main factors influencing the development of OC in Poland include cigarette smoking and excessive alcohol consumption. Tobacco use in any form (chewing, smoking) can lead to the development of cancer in the oral cavity and pharynx [3–5]. Smoking is estimated to be associated with a 7-fold increased relative risk of developing OC, and alcohol consumption >50 g/day is

associated with a 6-fold increased risk of developing OC [3]. Both stimulant users had a significantly increased risk of developing OC. The additive effect associated with alcohol consumption potentates the activation of procarcinogens present in tobacco. Alcohol abusers who are heavy smokers have a 38-fold greater risk of developing OC than non-users of either stimulant [6].

Another stimulant popular in Asian countries, used by about 20% of the world's population, that increases the risk of OC is betel (areca nut) chewing. According to a study, betel chewing increases the risk of OC mortality by approximately 12.5 times [7].

The risk of developing OC increases with age, and only about 6% of all OCs develop in patients younger than 45 or even 40 years of age. This approach applies mainly to patients with cancer of the mobile part of the tongue. Among these patients, approximately ¼ had not been exposed to any of the currently known risk factors. It is thought that in these people, the development of cancer may be caused by other yet unknown factors or have a viral basis, e.g. in the course of human papillomavirus (HPV) infection.

The human papillomavirus is a known aetiological factor in the development of oropharyngeal cancer [8]. Its role in the development of OC is controversial, but it is also thought to cause this type of cancer in younger subgroups of patients [9–10]. The most common virus types identified in OC were HPV-16 and HPV-18 [11–14]. The occurrence of HPV-associated cancers is associated with better prognosis [8].

Other viruses that may underlie cancer in the head and neck region are herpes virus (HSV) and Epstein–Barr virus (EBV). Lip cancers may be related to HSV infection. Its nucleic acids have been shown to be present in lip cancers, while antibody levels for HSV-1 and HSV-2 are greater in patients with lip cancer than in controls [15]. Furthermore, the presence of HSV in smokers is associated with an increased risk of cancer [16]. The Epstein–Barr virus may also be associated with the development of OC, but at this point, its role remains controversial [17–22].

Poor oral hygiene, bacterial and fungal infections causing periodontal disease are documented irritants in the oral cavity, which consequently constitute risk factors for the development of cancer in this area [23]. In the elderly, ill-fitting dentures that cause chronic irritation of the mucosa are an additional factor influencing the development of cancer, especially of the gums and tongue shafts [24].

Dietary factors also influence the development of OC. Freedman et al. showed that low fruit and vegetable intake was associated with an increased risk of head and neck cancer [25]. A Mediterranean diet has been shown to have a beneficial effect on reducing the risk of oral and oropharyngeal cancers [26].

Other aetiological factors include UV radiation (lip cancer), low socioeconomic status, ionising radiation and genetic syndromes associated with the impairment of genes responsible for DNA repair and induced cell death (e.g., Li Fraumeni syndrome, Fanconi anaemia), riboflavin and iron deficiency (Plummer-Vinson syndrome) and lupus and syphilis-like lesions [6, 27–28].

**Histology**

The oral cavity is highly exposed to external factors that can cause pre-cancerous lesions on mucous membranes that, over time, may develop into malignant tumours. These conditions include whitish (leukoplakia) and red patches (erythroplasia, erythroplakia), lichen planus and rhomboid tongue inflammation. Conditions directly leading to the development of malignancy include small-, medium- and high-grade squamous metaplasia or dysplasia and carcinoma in situ [27, 29–30]. SCC accounts for more than 90% of all OCs [31–32]. Other histopathological diagnoses, such as basaloid carcinoma and papillary carcinoma, are rare [33].

The lymphatic system draining the oral cavity is extremely extensive. The presence of cervical lymph node metastases is an important prognostic factor [34–36]. Although macroscopic cervical

lymph node metastases can be predicted to some extent by clinical staging, the probability of hidden neck lymph node metastases is high, ranging from 20% to 45% [37–40]. The submental and submandibular lymph nodes are the first stations of lymphatic metastasis, followed by the group II and III neck lymph nodes. Because of the crossed lymphatic drainage through the anterior group of submandibular nodes, OCs can metastasise bilaterally and even contralaterally [38]. Tumour cells originating from the OC may bypass the first or even the second metastatic station and move to more distant levels according to the so-called skip pattern of metastasis [41]. There is an internationally accepted consensus that removal of neck lymph nodes is generally recommended, especially if the risk of hidden metastases exceeds 15–20% [42–43]. Several studies have shown that the depth of primary tumour infiltration (DOI) proportionally influences the risk of cervical lymph node metastasis [37, 44].

A complete histopathological report after OC resection should, as a standard, include the histological type of tumour and its grade of differentiation, tumour dimensions, DOI, description of removed bony structures infiltration, assessment of neuroinvasion and angioinvasion, width of the surgical margins, number of lymph nodes removed, number of involved lymph nodes, presence of extranodal extension with the designation of nodal groups, and stage of pTN according to the current TNM classification (currently TNM 8th edition according to the AJCC) [45–47]. For the reliability of complete histopathological reports, adequately labelled preparations by the operating team are essential.

In modern histopathological diagnosis, which involves combining classical risk factors with molecular biology, new scales are being sought to assess personalised risk for patients. Such scales and new prognostic factors may include the type of infiltration (pattern of infiltration – POI) [48–49], assessment of the lymphocytic response (LHR) [50], assessment of the aggressive risk scale, tumour budding [51] and HPV status determination, especially in tumours also involving the oropharynx [52]. For immunotherapy, it is also necessary to determine the status of PD1 and PD-L1 in

histopathological material [53-54] or its equivalent. The combined positive score (CPS), which is defined as the sum of PD-L1-stained tumour cells and surrounding lymphocytes and macrophages divided by the total number of viable tumour cells multiplied by 100 [55], seems to be a standard procedure.

In recent years, there have also been tested a number of studies investigating the role of various genetic and molecular factors in postoperative material and surgical margins – including *PTEN* [56], *TIMP3*, *SFRP1*, *SFRP2*, *CDH1*, *RASSF1*, *RORA*, *DAPK1* [57], TIL – tumour-infiltrating lymphocytes [58] and many others [59–61]. However, a clear statement of their clinical utility requires further research.

**Diagnostic and treatment**

Diagnostic imaging – computed tomography (CT) scan of the head and neck with contrast to assess bone infiltration seems to be crucial prior to treatment decision-making. For the assessment of soft tissue infiltration and donor vessels for reconstructive surgery, contrast-enhanced magnetic resonance imaging (MRI) is indicated as the sole diagnostic tool or supplementation of CT scans. A chest X-ray or chest CT scan and abdominal ultrasound are also indicated to exclude the possibility of distant spread of disease. In patients with a higher risk of distant metastases positron emission tomography (PET) examination could also be considered. Careful laryngological examination of the oral cavity should not be omitted.

Surgery is the treatment of choice for patients with OC. Surgery involves resection of the primary tumor within the margins of healthy tissue with histopathological examination of the margins (intraoperative) and cervical lymphadenectomy to an extent appropriate for the disease stage (with intraoperative histopathological evaluation of the adjacent lymph node groups). Depending on the extent of resection, concomitant reconstructive surgery of the tissue defect should be considered – locoregional or free flap reconstruction [33].

Prehabilitation to prepare patients for aggressive treatment, often followed by a significant functional, energetic and metabolic burden, should always be considered. Prehabilitation includes assessment of nutritional status and prevention of malnutrition; psychological support and education about the disease; treatment methods; preoperative pharmaceutical care; and information about the patient's social benefits after treatment. After surgery, early rehabilitation of speech, swallowing and consumption of fluids and meals of different consistencies is crucial for further outcomes.

The indications for postoperative radiotherapy (pRT) include stage of the primary tumour (T3 or T4), regional lymph node involvement, nerve infiltration, blood vessel congestion and lymphatic vessel infiltration. Positive postoperative margins and extracapsular extension (ECE) for lymph nodes are indications for postoperative concurrent radiochemotherapy fractionated conventionally with platinum compounds [62–65].

Despite the above, clinical practice shows that, according to histopathological findings, almost all patients with OC after surgery require at least complementary RT. In selected cases with “save” postsurgical histopatological report, abandoning of complementary treatment could be considered. The patient's age, general performance status and additional medical conditions have to be assumed. On the one hand, age may be an indication to abandon RT, taking into account the side effects and the risk of a second cancer; on the other hand, our clinical experience shows that OC in younger patients can be extremely aggressive.

According to the National Comprehensive Cancer Network (NCCN) guidelines 2.2023, pRT should be started no later than 6 weeks after surgery. Conventional fractionated radiotherapy (RT) (2 Gy/fx), 5 days a week (Monday to Friday) over 6–6.5 weeks to a total dose of 60–66 Gy for areas at high risk of recurrence and to a dose of 44–50 Gy for elective areas is preferred. Intensity-modulated radiation therapy (IMRT) or 3-Dimensional Conformal Radiation Therapy (3D-CRT) is currently the technique of choice [66].

In advanced cases, despite pRT, the risk of locoregional recurrence and distant metastases is relatively high (5-year PFS 36%, 5-year OS 40% and 5-year LRC 69% [65]; incidence rate of DM, median 6.0% [67]). The risk increases with adverse prognostic factors according to postoperative histopathological examination. Risk factors include positive surgical margins [65, 68–71], lymph node metastases with ECE [62–63, 68–74], perineural infiltration [62, 75], and cancer cell emboli in blood vessels [75]. To reduce the risk of failure in this group of patients, postoperative chemoradiotherapy (CHRT) should always be considered.

Cooper et al. (2004) showed that the addition of chemotherapy (CHT) to pRT significantly prolonged DFS (HR for disease or death 0.78; P=0.04) but had no effect on OS (HR for death 0.84, p = 0.19) [65]. Similarly, Bernier et al. (2005) showed that the addition of CHT to high-risk groups at the 5-year follow-up significantly prolonged PFS (47 *vs*. 36%) and OS (53 *vs*. 40%) without significantly increasing late adverse effects [64].

Definitive RT or brachytherapy (BT) (when anatomically feasible and at a low stage – T1, possibly T2, without lymph node spread) could be considered as a less effective primary treatment alternative to surgery when surgery is not feasible or the patient does not consent. For definitive RT, the NCCN guidelines 2.2023 outline three possible fractionation modalities – standard RT fractionation to a total dose of 66–70 Gy (2 Gy/fraction), 5 days a week to the primary tumour area and metastatic lymph nodes; RT with concomitant boost – 72 Gy in 6 weeks – 1.8 Gy per fraction to large fields and 1.5 Gy boost as a second daily fraction during the last 12 days of treatment or RT 66–70 Gy for 6 days a week or hyperfractionated RT – 81.6 Gy over 7 weeks (1.2 Gy/fraction, twice daily). For radical BT, the NCCN suggests LDR brachytherapy (0.4–0.5 Gy/h) as a boost to external-field RT to a total dose of 50 Gy or alone to a total dose of 60–70 Gy or HDR BT – a 21 Gy boost in 3 fractions combined with external-field RT to a dose of 50 Gy or as a single treatment – 45–60 Gy in 3–6 Gy fractions [66]. However, RT to high, curative doses only in selected cases is applicable due to proximity of the maxilla and the high risk of bone necrosis.

As an alternative method for external beam boost in patients with early-stage of disease the use of intraoperative radiotherapy (IORT) at a single dose of 5–7.5 Gy, followed by external beam radiotherapy up to 50 Gy could be considered [76].

In the literature, 5-year OS for patients with OC after pRT ranges from 59% to 70%. Survival rates may vary depending on the anatomical location of the various subsites, stage, grade of OC, age at diagnosis, treatment and comorbidities [77].

In patients with initially unresectable tumours, induction chemotherapy (indCHT) could be an option. Despite the often observed clinical benefit, the efficacy of such treatment has not been proven in randomised clinical trials [78–80]. In general, the results of treatment in this group of patients are suboptimal, and clinical trials to search for new, more effective treatments are needed.

Examples of such trials are described below. The most promising clinical trials available for patients with operable OC include GORTEC 2018-01 (NIVOPOSTOP), the MK-3475-689 trial and the MS202359-0002 trial.

GORTEC 2018-01 (NIVOPOSTOP) is a randomised phase III clinical trial evaluating postoperative adjuvant therapy with nivolumab concomitantly with CHRT in high-risk patients following radical surgery. Nivolumab starts 3 weeks before CHRT and is continuing in the dose of 360 mg on days 1, 22 and 43 of CHRT. After completion of CHRT, nivolumab alone is administered as maintenance treatment. In the control arm, patients receive standard CHRT with 100 mg/m$^2$ cisplatin on days 1, 22 and 43 of RT [81].

In another phase III study, pembrolizumab is given twice every 3 weeks prior to surgery, and is continuing in combination with RT or CHRT after surgery (MK-3475-689). In another randomised double-blind phase III clinical trial after surgery, patients receive xevinapant and RT when platinum-derived compound is contraindicated. In this study, in the experimental arm, patients receive 3 cycles of xevinapant at a dose of 200 mg/day once daily from day 1 to day 14 in a 3-week cycle in combination with RT followed by 3 cycles of xevinapant (1 to day 14) in a 3-week cycle (each cycle

lasts 3 weeks). In the control arm, a placebo is used in the same way [82]. In patients who have relapsed after radical treatment, salvage surgery is the treatment of choice. The 5-year OS rate after salvage surgery ranges from 10–74% and depends largely on risk factors, mainly the presence of nodal recurrence and prior treatment. Better results are observed in younger patients without nodal recurrence and those who did not received RT as primary treatment [83–84]. When surgery is not possible, stereotactic RT is attempted, limited by the radiation dose previously received. Vargo et al., in a multicentre study of SBRT for recurrent or second primary head and neck cancer showed a 2-year patient survival rate of 16.3% [85].

There are two studies summarising the clinical outcomes of repeat salvage irradiation with curative intent for unresectable recurrent squamous cell carcinoma of the head and neck - the RTOG 96-10 and RTOG 99-11 trials, which investigated reirradiation with concurrent chemotherapy [86–87]. Previous RT in eligible patients should be terminated at least 6-month earlier. The results of these studies highlight the uncertain prognosis for patients with recurrent disease treated with re-irradiation with 2-year OS rates of 15.2% in RTOG 96-10 patients and 25.9% in RTOG 99-11 patients. Unfortunately, only 20–30% of patients with primary treatment failure are candidates for salvage surgery or RT [88]. For these patients, palliative systemic treatment or best supportive care is the only option. An approximately 30% response rate and median progression-free survival (PFS) of 3 to 4 months and a median overall survival (OS) of 6 to 8 months could be obtained with platinum combined with fluorouracil or a taxans [89–90]. EXTREME trial with cetuximab, an inhibitor of epidermal growth factor receptor (EGFR) added to a platinum-based chemotherapy with fluorouracil significantly increased PFS from 3.3 to 5.6 months and median OS from 7.4 months to 10.1 months compared to chemotherapy alone [91]. KEYNOTE-048 trial showed that patients with metastatic H&N cancer or recurrent H&N may benefit from pembrolizumab given alone (when slow progression without clinical symptoms is observed) or when it is combined with platinum and fluorouracil (for quick progression and/or aggravated clinical symptoms of this tumor) when the combined positive score (CPS) $\geq$1 has been found [92]. The results of this trial showed a statistically significant increase

in 2-year overall survival (OS) to 31% for patients treated with the combination of pembrolizumab with chemotherapy versus 17% for patients treated with standard treatment (cetuximab with chemotherapy) [92]. Monotherapy with docetaxel, methotrexate or cetuximab for several years was the only therapeutic option for those who failed first-line palliative chemotherapy. Currently, for second-line treatment nivolumab could be used according to the results of the CheckMate study 141. This study showed a statistically significant improvement in OS (1-yr 36.0% *vs.* 16.6% in favour of nivolumab compared with standard treatment) in patients randomised to the nivolumab group compared with the investigator-selected treatment group, as well as a significant increase in response time (median 9.7 months *vs*. 4.0 months) [93].

For recurrent or untreated OC and primary disseminated cancers, various clinical trials are also being conducted to improve the results. [94–100]. Current trials evaluate the efficacy of other drugs, such as lenvatinib in combination with pembrolizumab versus pembrolizumab monotherapy, GSK3359609 or placebo in combination with pembrolizumab or a comparision of BNT113 in combination with pembrolizumab versus pembrolizumab monotherapy [94–96].

For distant dissemination in oligometastatic disease, the treatment of choice is also primary surgery or, if ineligible, stereotactic radiotherapy. Preliminary results from the SABR-COMET trial of ablative stereotactic radiotherapy in patients with up to five metastatic sites from any primary tumour site showed improved progression-free survival (12 *vs*. 6 months, $p < 0.01$) and overall survival (41 *vs*. 28 months, $p = 0.09$) when metastatic sites were treated with irradiation [97]. Sun et al. simulated 5-year survival rates of 20% in selected patients with head and neck cancer who underwent oligometastasis surgery with stereotactic irradiation of metastases [98].

In symptomatic patients with poor performance status who are not eligible for surgery, palliative radiotherapy remains the treatment of choice. Mohanti et al. described similar weekly treatment in a large retrospective study involving 505 patients. Patients were treated with a dose of 20 Gy in five fractions. Symptom relief was obtained in 47%-59% of the patients following palliative

RT [99]. Compared to the Fortin et al. study, in which patients were treated with a dose of 25 Gy in 5 fractions, this regimen showed a lower objective response rate of 50% [100]. Furthermore, all patients in this cohort developed patchy mucositis at follow-up 1 month after treatment.

**Conclusions**

There is an urgent need to develop new, more effective treatment methods for oral cancer patients. In this context, the role of immunotherapy as well as targeted therapies should be more extensively investigated. Several ongoing clinical trials evaluate novel therapeutic approaches, such as immune checkpoint inhibitors (e.g. nivolumab, pembrolizumab), monoclonal antibodies (cetuximab), small molecule inhibitors (lenvatinib) or cancer vaccines (BNT113).

Moreover, further research is warranted to establish new prognostic and predictive factors, as well as disease and patient stratification models. These could enable personalized therapy tailored to the biological characteristics of the tumor and the patient. Genetic and molecular analyses seem especially interesting in this matter.

Special attention should also be paid to better understanding of oral cancer etiopathogenesis. The role of HPV infection, but also other potential viral factors requires further elucidation. Additionally, promotion of healthy lifestyles and reduction of risk factor exposure in the general population could contribute to oral cancer prevention on the public health level.

In summary, advancing the diagnostics and treatment of oral cancer calls for a coordinated effort from various fields of clinical medicine and basic science. Only multidirectional research and multidisciplinary collaboration can bring a significant improvement in the outcomes of patients affected by this disease.

## Article information and declarations

## *Conflict of interst*

None declared

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