

Treatment of advanced laryngeal and laryngopharyngeal cancer - literature review and the author's own experience

Leczenie zaawansowanego raka krtani i krtaniowej części gardła – przegląd literatury i doświadczenia własne

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Article history: Received: 15.04.2018 Accepted: 16.05.2018 Published: 30.06.2018

ABSTRACT:

As many as 70-85% of laryngeal and laryngopharyngeal cancers are diagnosed at a high staging, comprising a great diagnostic and therapeutic challenge with influence on poor treatment results. Patients with advanced lesions, that is, stages III and IV, qualify for primary surgical treatment or chemoradiotherapy, depending on the clinical stage, poor prognostic factors and preferences of the patient. Reliable qualifications standards for treatment that would allow to establish homogenous therapeutic recommendations and improvement of treatment results in the group of patients have not yet been developed.

KEYWORDS:

laryngeal cancer, hypopharyngeal cancer, locoregional recurrence, adjuvant chemoradiotherapy, head and neck squamous cell carcinoma

STRESZCZENIE:

Aż 70–85% nowotworów krtani i krtaniowej części gardła jest rozpoznawanych w wysokim stadium zaawansowania, stanowiąc duże wyzwanie diagnostyczno-terapeutyczne i wpływając na złe wyniki leczenia. Chorzy ze zmianami zaawansowanymi, w stadium III i IV, kwalifikowani są do pierwotnego leczenia chirurgicznego lub chemioradioterapii – w zależności od stopnia zaawansowania choroby, czynników złego rokowania i preferencji chorego. Brakuje jednak wypracowanych wiarygodnych standardów kwalifikacji do leczenia, które pozwoliłyby na ustanowienie jednolitych zaleceń terapeutycznych oraz poprawę wyników leczenia w tej grupie chorych.

SŁOWA KLUCZOWE:

rak krtani, rak krtaniowej części gardła, wznowa miejscowa, adjuwantowa chemioradioterapia, rak regionu głowy i szyi

INTRODUCTION

Squamous cell carcinoma accounts for 95% of all malignant tumors in the head and neck. 3-5% of them are located in the larynx and hypopharynx. In 70-85% of cases, tumor is diagnosed at an advanced stage, which is associated with an unfavorable prognosis: average 5-year survival oscillates between 15-45% [1, 2]. The group of patients with diagnosed laryngeal and hypopharyngeal cancer is dominated mainly by men (male to female ration - MFR- 4:1) in their fifth and sixth decade of life, tobacco smokers,

very often with overuse of spirits, with low pro-health awareness, often internally burdened [22]. A delayed visit at the doctor's with symptoms indicating towards significant advancement of tumor make the diagnostic-therapeutic process complicated and pose a big challenge, that does not always end with success.

CHOICE OF THERAPEUTIC REGIMEN

In patients with low-grade laryngeal and hypopharyngeal can-

Tab. I. Classification of staging of laryngeal and hypopharyngeal tumors as per TNM Classification of Malignant Tumors 8th Edition [19].

STAGE	CECHA T	CECHA N	CECHA M
Step 0	Stage 0	No	Mo
Stage	T1	No	Mo
Stage II	T2	No	Mo
Stage III	T3	No	Mo
	T1, T2, T3	N1	Mo
Stage IVa	T4a	No, N1, N2	Mo
	T1, T2, T3	N2	Mo
Stage IVb	T4b	Every N	Mo
	Every T	N3	Mo
Stage IVc	Every T	Every N	M1

cer (Stage I-II), the preferred method of choice is endoscopic surgery that allows to remove the tumor with a rim of healthy tissues and retain the function of the larynx. Comparable therapeutic results are obtained with initial radiation therapy. The second method, according to data from literature, allows to retain better voice quality after convalescence, therefore the choice of treatment should be discussed with the patient in detail after presenting the benefits and complications resulting from each possible therapeutic option [3].

In the case of advanced tumors (Stage III-IV), there is lack of unambiguous, reliable guidelines that regards the choice of initial treatment. Possible patterns are based either on surgical resection of tumor with adjuvant radiotherapy or chemoradiotherapy, or primary, radical chemoradiation, that the results of treatment are comparable. However, it should be noted that continuous and dynamic development of radiotherapy methods, surgical techniques and the availability of new molecular targeted drugs for systemic therapy (monoclonal antibodies, immunotherapy) require constant verification of the optimal choice of treatment protocol in this group of patients [4, 5, 21, 23].

SURGICAL TREATMENT IN LARYNGEAL AND HYPOPHARYNGEAL CANCER STAGE III-IV

Patients who report to a laryngologist with advanced pharyngeal and hypopharyngeal tumor, depending from the exact tumor location, its size and infiltration of surrounding tissues are suggested extensive procedures that are aimed at removal of lesion with a rim of healthy tissues, often times requiring simultaneous reconstruction to preserve continuity of digestive tract (laryngopharyngectomy, total laryngectomy with a partial pharyngectomy, partial laryngectomy with a partial pharyngectomy).

Surgical resection is the treatment of choice in the group of patients in whom imaging studies show an infiltration into laryngeal cartilages, disqualifying them from initial treatment which allows to preserve the organ. Due to significant advancement of neoplastic disease in patients with stage III and IV, qualification for adjuvant radiation therapy is recommended to ensure radicality of treatment and better local control [4].

It seems that initial, radical resection of the lesion allows to obtain a longer period free of locoregional relapse and extension of overall survival time in comparison to initial treatment with chemoradiotherapy. In their study, Iyer et al. proved that initial surgical treatment allows to extend the general survival rate in patients and the disease free period. In the group of patients subject to initial chemoradiotherapy treatment, there is better local control of disease and rarer prevalence of distant metastases. However, these observations are not supported by results of statistical analysis. What is more, there are no multicenter, randomized clinical trials to statistically confirm the above observations and reliable meta-analyses that would allow to establish general standards for treatment of this group of patients [21, 25].

Due to the dynamical growth of new surgical branches such as microsurgery, laser surgery or robotic surgery (Transoral Robotic Surgery- TORS), there is an increasingly better treatment outcome in patients with tumor of the larynx and hypopharynx, as well as improvement in functionality results after surgery, especially in patients with an early-stage cancer [6].

ADJUVANT CHEMORADIO THERAPY

Adjuvant treatment should begin within 6 weeks of surgery to achieve the best therapeutic results. Depending on the presence of factors of poor prognosis, such as infiltration of perilaryngeal tissues, nerve and vascular infiltration, the presence of tumor cells in small vessels or the presence of pericapsular infiltration in the case of lymph node metastases, the standard total radiation dose may vary between 50-66 Gy and is divided into fractions spread over a period of 6 weeks. Regional treatment may be combined with a systemic one, based on the administration of 100 mg/m² platinum salt in 3 cycles on days 1, 22 and 43 from the beginning of radiotherapy [7].

RADICAL CHEMORADIO THERAPY IN ADVANCED LARYNGEAL AND HYPOPHARYNGEAL CANCER

Choice of treatment with radical chemoradiotherapy should be preceded by necessary imaging and endoscopic tests to assess

Tab. II. Prognostic factors in patients with laryngeal and hypopharyngeal tumor based on UICC Manual of Clinical Oncology, 9th Edition [20].

PROGNOSTIC FACTORS	CONNECTED WITH TUMOR	CONNECTED TO PATIENT	SOCIO-ENVIRONMENTAL
Key	TNM advancement, Pericapsular infiltration	Concomitant diseases, Age > 70 years old, General condition at diagnosis	Availability for treatment, Quality of available therapy
Additional	Number of lymph node groups involved, Tumor volume, Paralysis of vocal folds, Tracheostomy	Sex, Degree of impaired laryngeal function	Nutrition, Total time of treatment for cancer
New	Cell markers: TP53, VEGF, EGFR, BCL 2, Amplification of coding region for cyclin D1, HPV status, Genes of chemoresistance	Quality of life at diagnosis	Availability of endoscopic laryngeal examination

the extent of neoplastic disease, which directly affects the choice of doses and treatment protocol. More and more attention is paid to the need for F-18 FDG positron emission tomography (18 FDG PET-CT), which allows both to assess locoregional advancement of neoplastic disease, but also to exclude distant metastases. It is estimated that even in as many as 15% cases, following PET-CT scan, it is necessary to modify initially suggested treatment schedule [8].

When qualifying patients for initial therapy with radical chemoradiation due to the possibility of preserving the larynx, one should always remember that saving the organ is not synonymous to preserving its physiological functions, which include swallowing and phonation. In many cases before the beginning of treatment, patients require tracheostomy and nutritional gastrostomy. Choice of radical chemoradiotherapy in patients who did not experience loss of laryngeal function as initial treatment may allow to obtain results comparable to surgical treatment as well as shorten the total time of initial treatment [9].

Initial surgical treatment is preferred in patients, in whom the tumor is destroying the cartilage, is very extensive and infiltrates into perilaryngeal tissues with diagnosed metastases in the neck lymph nodes. In these cases, radical resection of initial tumor and cervical lymph nodes is associated with simultaneous reconstruction of the hypopharynx in order to retain continuity of the digestive tract. As a result of such treatment, patients can swallow food without the risk of its aspiration to the airways, and the voice can be reproduced using a voice prosthesis [10].

INDUCTION CHEMOTHERAPY IN ADVANCED LARYNGEAL AND HYPOPHARYNGEAL CANCER

One of the proposed methods of treatment and determination of potential chemoradiosensitivity of primary tumor is induction chemotherapy. Treatment protocol are most often based on one-off administration of a chemotherapy cycle based on platinum derivatives, 5-fluorouracil and docetaxel followed

by assessment of tumor regression in imaging and endoscopy after 21-28 days. Patients with good tolerance of treatment and significant decreasing of tumor size due to high chemoradiosensitivity of cancerous cells can be subject to radical chemoradiotherapy with lack of contradictions. However, Nakashima et al. point to the fact that treatment that begins with induction chemotherapy should be dedicated to a selected group of patients due to its high toxicity, which may lead to neutropenia, severe anemia, cholestasis and induce dyspnea.

What is more, induction chemotherapy should not be performed routinely, and rather reserved for clinical study which has been subject to a positive opinion by a bioethics committee. There are only a few papers on the results of induction systemic therapy combined with radical chemoradiotherapy in patients with advanced head and neck cancer, and complications resulting from significant toxicity of such a protocol may significantly affect the quality of life in patients, unrelated to the neoplastic disease itself [11, 12].

TREATMENT OF LOCAL RECURRENCES

The treatment of choice in the case of local recurrence of primary tumor in patients previously treated surgically in combination with adjuvant therapy or by radical chemoradiotherapy is surgical resection with reconstruction by pedicle flaps or free flaps with vascular microanastomosis [13, 24].

Due to lack of unequivocal standards, in some clinics patients who have been disqualified from surgical treatment are qualified for palliative chemoradiotherapy, however, it seems that such management is burdened with very high risk of complications. Particular attention is paid to the greater toxicity of re-treatment and risk of severe carotid artery damage due to irradiation [14].

Use of platinum salt derivatives in systemic palliative treatment in combination with monoclonal antibodies directed against the epithelial growth receptor (anti-EGFR) allows for

longer overall survival compared to regimens based only on administration of platinum salt [15]. Attention is also paid to the possibility of palliative chemotherapy in the group of patients with recurrences, which is based on the combination of platinum, docetaxel, 5-fluorouracil and cetuximab salts administered in small doses. Such a treatment regimen allows to reduce toxicity of treatment, as a result of which it is possible to extend the time of its administration [16].

There are clinical trials aimed to use the monoclonal antibody directed against the PD-1 receptor (Nivolumab- Opdivo®) in treatment of patients with recurrent squamous cell carcinoma of the head and neck. The clinical trial CheckMate 141 which assessed efficiency of treatment in patients with recurrence extended the overall survival in the case of therapy that contained Nivolumab in comparison to a standard treatment regimen based on one cytostatic drug [17].

The available works also draw attention to the possibility of using proton therapy in the group of patients with local recurrence of primary tumor who have undergone previous irradiation, however, the availability of such treatment is very limited due to the small number of centers and lack of systemic financing. What is more, we do not hold clinical standards elaborated and verified in treatment for qualification of patients for such therapy [18].

PROTOCOL OF THE POLISH SOCIETY OF OTOLARYNGOLOGISTS - HEAD AND NECK SURGEONS

In order to maintain uniform, high standards of treatment of patients with laryngeal and hypopharyngeal cancer, the Polish Society of Otolaryngologists - Head and Neck Surgeons has developed recommendation for treatment in patients with head and neck cancer. These recommendations, based on global guidelines, are generally available and regularly updated.

They draw attention to the need for a meticulous diagnostic process, with performance of necessary imaging examinations (neck ultrasound, computed tomography and magnetic resonance), specialist consultations (internist, anesthesiology, nutrition and rehabilitation) and surgical biopsy to histopathological evaluation (microlaryngoscopy), which allows to make a diagnosis, assess the extent of neoplastic process and qualify for treatment. In the case of patients who report with a significant staging of advancement (III-IV), it is indicated to perform PET-TC and panendoscopy, in the group of patients with lesions located in the supraglottic region, which go beyond its anatomical border and in the case of tumor of posterior cricoid region, which may infiltrate the esophagus.

The recommended method of initial treatment in stage III and IVa is surgical treatment for radical tumor resection, especially in patients with destruction of cartilaginous structures of the larynx, infiltration >1 cm in root of tongue. In case of reconstruction, it is recommended to use pedicle flaps or free flaps with vascular microanastomosis to restore the continuity of digestive tract. If the patient does not agree to initial surgical treatment, it is possible to conduct radical chemoradiotherapy, but this is recommended in the group without infiltration into the cartilaginous structures of larynx.

Recommendations for removal of lymph nodes depend from initial tumor location, its size (feature T) and presence of nodal metastases (feature N). In the lesion initially located in the hypopharyngeal or supraglottic region, routine removal of lymph nodes is recommended (elective, selective or radical treatment depending on the T and N feature) with accompanying adjuvant radio- or chemoradiotherapy. Supplementary treatment may be omitted in the group of patients with a lesion localized primarily in glottic or infraglottic region, when there is no tumor metastasis in electively removed lymph nodes and lack of microscopic signs, which negatively impact prognosis.

AUTHOR'S OWN EXPERIENCE

Department of Otolaryngology of the Medical University of Warsaw has many years of extensive experience in the surgical treatment of head and neck cancer. Patients with laryngeal cancer, depending on the severity of disease, are treated endoscopically with laser surgery, surgery to completely remove the larynx, hypopharynx, cervical part of esophagus, neck lymph nodes using tissue reconstruction methods in cases of significant deficits. The adopted management guidelines in advanced laryngeal and hypopharyngeal cancer are as follows: accurate diagnosis to determine the extent of cancer, presence of lymphatic and/or distant metastases and the second initial foci, surgical treatment: most often en bloc organ removal with neck lymph nodes (due to the severity of disease, it is usually Crile's operation) and in cases of extensive tissue resection, reconstructive surgeries. To reconstruct the digestive tract, free autografts are used to close partial tissue deficits (forearm island skin and fascia flap) or total (autograft fragment of the small or large intestine or skin and forearm fascial flap). Patients are subject to adjuvant radiotherapy. Surgical treatment is increasingly used in patients after previous oncological treatment: chemoradiation as "salvage surgery". However, this treatment is burdened with significant risk of complications in perioperative period and during the healing period.

SUMMARY

Advanced laryngeal and hypopharyngeal cancer is most often diagnosed in the group of patients with numerous burdens (age, concomitant diseases), which hinders initial qualification for treatment and deteriorates therapeutic results. There is lack of elaborated, reliable therapeutic standards, which is associated with the need to perform extended internal medical diagnosis, advancement of neoplastic disease at the moment of qualification for treatment and making a decision regarding the choice and regime

of initial treatment as part of consultations with specialists in the fields of surgery (laryngologist, maxillofacial surgeon, oncologist surgeon), radiology, nuclear medicine, oncology and radiotherapy. Despite intensive development of new surgical techniques (microsurgery, robotic surgery, reconstructive surgery) and availability of advanced radiotherapy methods combined with systemic treatment, therapeutic results are comparable, therefore when making a decision, one should also take into account the availability of suggested treatment, general condition of patient, predicted functional results and life quality after end of therapy.

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Word count: 2050 Tables: 2 Figures: – References:24

Access the article online: DOI: 10.5604/01.3001.0012.0993 Table of content: <https://otorhinolaryngologypl.com/issue/11162>

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Competing interests: The authors declare that they have no competing interests.

Cite this article as: Krawczyk P, Osuch-Wójcikiewicz E., Majszyk D., Bruzgielewicz A., Niemczyk K.: Treatment of advanced laryngeal and hypopharyngeal cancer - literature review and the author's own experience; Pol Otorhino Rev 2018; 7(2): 25-30
