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REVIEW ARTICLE

Updated National Comprehensive Cancer Network guidelines for treatment of head and neck cancers 2010-2017

Authors' Contribution:
A – Study Design
B – Data Collection
C – Statistical Analysis
D – Data Interpretation
E – Manuscript Preparation
F – Literature Search
G – Funds Collection

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ABSTRACT:

Introduction: The diagnostic and therapeutic recommendations have been changing over the years to improve treatment outcomes and quality of life of Head and Neck Cancer (HNC) patients.

Aim: The aim of this study was to present currently recommended Head and Neck Cancer treatment guidelines based on the literature review with particular emphasis on novel approaches the NCCN algorithms.

Material and methods: The review of literature covering articles published in the last five years and pointing out essential changes in HNC treatment regarding evidence based medicine. The study focused on the analysis of novel approaches for the particular primaries, the implementation of biological therapies and personalized cancer therapies.

Results: Updates in the oncological NCCN guidelines for all ENT primaries except major salivary glands and subglottis are based on knowledge derived from the basic sciences, clinical trials and the best evidence available currently. The latest recommendations emphasize value of biological therapies use.

KEYWORDS: head and neck cancers treatment guidelines, biological therapy, personalized treatment, recommendations

INTRODUCTION

Head and neck cancer (HNC) is the sixth most common cancer type. In 2012, HNCs were diagnosed in over 500,000 people worldwide, and over 90% of HNCs are squamous cell carcinomas [1,2]. In Poland, HNCs and cancers of the eye and the central nervous system comprise 11% of all cancers in men and 7.5% in women; in the early 1990s, these figures were 14% for men and 6.7% for women [3,4]. The choice of treatment for HNCs depends on primary cancer location, cancer stage, and previous treatments.

Guidelines of the National Comprehensive Cancer Network (NCCN) were first published in Poland in 2006 in the "Advances in Head and Neck Surgery" [5] and then updated in 2011 in the "Polish Otorhinolaryngology Review" [6]. These guidelines gave important information on HNCs, and they helped in diagnosing and treating patients with different locations of HNCs; moreover, the guidelines described in detail postoperative follow-up [6,7].

In this article, we describe current evidence regarding diagnosis and treatment of HNC, and we present new NCNN guidelines for treatment of HNCs.

MATERIALS AND METHODS

We reviewed studies published over the last 5 years and described key evidence-based changes in treatment of HNCs. We disregarded experimental studies and case reports. We focused on the NCCN guidelines published in 2010 and 2016. We analyzed new treatments for different primary HNC sites, biological therapies, and personalized therapies.

RESULTS

Tables I, II, and III present changes in treatment guidelines for laryngeal cancers located in the glottis, epiglottis, and lower pharynx. Regarding treatment guidelines for laryngeal cancers

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Tab. I. Changes of treatment guidelines for glottal cancer.

NCCN GUIDELINES, HEAD AND NECK CANCERS 2010	NCCN GUIDELINES, HEAD AND NECK CANCERS 2017
Tis -> decortication	Tis -> decortication or radiation therapy
T1,T2 -> larynx-preserving surgery or radiation therapy	also for selected T3 cancers
After selective lymph node dissection if risk factors present -> radiation therapy	ECS -> radiochemotherapy
For T4aN0 cancers -> adjuvant radiation therapy or radiochemotherapy (in addition to treatment of the primary cancer location)	Positive margins -> repeated resection or radiation therapy
T4b palliative treatment	Remaining risk factors -> radiation therapy
	One-sided or two-sided lymph node dissection can be performed before radiation therapy or radiochemotherapy
	PS 0-1 radiochemotherapy or induction chemotherapy with subsequent radiation therapy or radiochemotherapy
	PS 2 definite radiation therapy +/- chemotherapy
	PS 3 palliative radiation therapy or single-drug chemotherapy or palliative treatment

located in the glottis or epiglottis, larynx-preserving treatment was extended to patients with stage T3 HNCs. In patients with stage 4 HNCs, induction chemotherapy, and in those with glottal cancers, also adjuvant chemotherapy can be considered. Treatment guidelines for subglottal cancers did not change.

The guidelines strongly recommend that patients with nasopharyngeal cancer undergo Epstein-Barr virus (EBV) screening (Table IV), and patients with oropharyngeal cancer, human papilloma virus (HPV) screening (Table VI). Moreover, patients with nasopharyngeal, oropharyngeal, and low-stage (T1, T2) oral cancer should undergo biopsy of sentinel lymph nodes (Table V). Treatment guidelines for salivary gland cancers did not change significantly. Treatment of maxilloethmoidal cancers depends on tumor location, and patients with suprastructure cancers have worse prognosis than those with infrastructure cancers. As regards melanomas of the mucous membranes, the greatest possible resection remains the indicated treatment, but clinical trials should be additionally offered to patients with melanomas of the mucous membranes.

Single modality treatment, i.e., surgery or radiation therapy, is indicated for tumors with low locoregional involvement. In patients with HNCs, combining different treatments or using new treatments, such as biological therapies, may lead to preservation of organ function and better quality of life [8,9].

In contrast to chemotherapy or radiation therapy, biological therapies use molecules that occur naturally in the human body. For instance, adoptive immunotherapy uses cytokines, growth factors, monoclonal antibodies, or gene therapy [10].

Tab. II. Changes of treatment guidelines for epiglottal cancer.

NCCN GUIDELINES, HEAD AND NECK CANCERS 2010	NCCN GUIDELINES, HEAD AND NECK CANCERS 2017
T1,T2 -> larynx-preserving surgery or radiation therapy	also for selected T3 cancers
T1-T3 N+ -> lymph node dissection	If one positive lymph node present without risk factors -> consider radiation therapy
T1-T, N0 -> elective lymph node dissection	T1-T3 N0 -> follow up

Tab. III. Changes of treatment guidelines for cancers of the lower pharynx

NCCN GUIDELINES, HEAD AND NECK CANCERS 2010	NCCN GUIDELINES, HEAD AND NECK CANCERS 2017
T1 -> larynx-preserving surgery	also for selected T2 cancers
T1-T3 N0 -> elective lymph node dissection	T2-T3 N0-N3 and T1 N+ -> lymph node dissection (including region VI)
T4a N0-3 -> surgery or radiochemotherapy	induction chemotherapy was added

In 2006, the Food and Drug Administration (FDA) approved cetuximab as an adjuvant to radiation therapy for patients with newly diagnosed and locally advanced head and neck squamous cell carcinoma (HNSCC) and for patients with recurrent or metastatic HNSCC (R/M HNSCC) who underwent chemotherapy with a platinum-based drug. In 2011, the FDA approved a cetuximab-based regimen (cetuximab + platinum-based chemotherapy + 5-fluorouracil [5-FU]) as a first-line treatment for w R/M HNSCC [11]. Cetuximab is an IgG1 monoclonal antibody against the endothelial growth factor receptor (EGFR), which is involved in cancer cell pro-

Tab. IV. Changes of treatment guidelines for nasopharyngeal cancer.

NCCN GUIDELINES, HEAD AND NECK CANCERS 2010	NCCN GUIDELINES, HEAD AND NECK CANCERS 2017
Search for metastases	Especially in non-keratinizing cancers, endemic phenotypes, and N2-N3 cancers Consider EBV/DNA screening Consider consultation with an ophthalmologist and/or endocrinologist
T2 No Mo T1-2 N1-N3 Mo T3-4 No-3 Mo -> radiochemotherapy or induction chemotherapy with subsequent radiochemotherapy	Radiochemotherapy with subsequent chemotherapy was added
No regression of primary cancer or its progression –> brachytherapy +/- chemotherapy	No regression of primary cancer or its progression –> contrast-enhanced CT and/ or contrast-enhanced MRI in 4 to 8 weeks : – Positive result -> tumor resection and/ or lymph node dissection – Negative result -> follow up

liferation, angiogenesis, apoptosis, migration, adhesion, and metastasis [12-14]. Cetuximab blocks binding of ligands to the EGFR, which inhibits EGFR function and leads to receptor internalization and reduced expression. Importantly, in patients with HNCs, high EGFR expression is associated with worse prognosis [12,15]. Moreover, cetuximab enhances lymphocyte-dependent cytotoxicity against cells expressing the EGFR (antibody dependent cell-mediated cytotoxicity) [12].

Monoclonal antibodies against immune checkpoint inhibitors show promise for patients with cancers that do not respond to standard treatments. These antibodies were developed because HNSCCs often lead to immune dysfunction [15,16], which promotes survival of cancer cells. For instance, the programmed cell death protein 1 (PD-1), a cell receptor and an immune checkpoint inhibitor expressed on activated CD4+ and CD8+ T cells, when activated by one of its two ligands (PD-L1, PD-L2), inhibits T cell activation and thus reduces inflammatory reactions [17]. Because cancer cells activate immune checkpoint inhibitors, such as PD-1, the host immune cells do not attack cancer cells [12].

In 2016, the FDA approved pembrolizumab, another biological drug and the first monoclonal antibody against immune checkpoint inhibitors, for patients with R/M HNSCC that do not respond to platinum-based chemotherapy. Pembrolizumab binds to the PD-1 receptor and thus blocks its interaction with PD-L1 and PD-L2 [18]. An accelerated approval to use pembrolizumab in patients with advanced HNCs was based on the phase Ib KEYNOTE-012 study, in which 82% of patients had a significantly prolonged response to pembroli-

Tab. V. Changes of treatment guidelines for oral cancer.

NCCN GUIDELINES, HEAD AND NECK CANCERS 2010	NCCN GUIDELINES, HEAD AND NECK CANCERS 2017
T1-T2 No -> surgery + elective lymph node dissection (optional for T1No)	T1-T2 No -> surgery +/- sentinel node biopsy: – no sentinel node identified-> lymph node dissection – sentinel node positive - > lymph node dissection – sentinel node negative and no risk factors -> follow up

Tab. VI. Changes of treatment guidelines for oropharyngeal cancer.

NCCN GUIDELINES, HEAD AND NECK CANCERS 2010	NCCN GUIDELINES HEAD AND NECK CANCERS 2017
	HPV screening recommended
T2 No-N1 -> surgery or radiation therapy or radiochemotherapy	Radiochemotherapy only in T2 N1
T4b N+ -> radiochemotherapy	– PS 0-1 radiochemotherapy or induction chemotherapy/ radiation therapy or radiochemotherapy – PS 2 RT +/- chemotherapy – PS 3 palliative radiation therapy or single-drug chemotherapy or palliative treatment

Tab. VII. Changes of treatment guidelines for lip cancer.

NCCN GUIDELINES HEAD AND NECK CANCERS 2010	NCCN GUIDELINES HEAD AND NECK CANCERS 2017
T1-T2 No surgical removal of the lesion or radiation therapy	(added) Consider surgical removal of the lesion +/- sentinel node biopsy: – no sentinel node identified-> lymph node dissection – sentinel node positive - > lymph node dissection – sentinel node negative and no risk factors i -> follow up

Tab. VIII. Changes of treatment guidelines for maxillary cancer

NCCN GUIDELINES HEAD AND NECK CANCERS 2010	NCCN GUIDELINES HEAD AND NECK CANCERS 2017
Contrast-enhanced CT or contrast-enhanced MRI	Additionally, PET-CT for grade III and IV tumors
T2 No, free margin -> consider radiation therapy selective lymph node dissection	T2 No, free margin -> follow up
T1-T2 No cystadenocarcinoma -> surgery and consider radiation therapy	T1-T2 No cystadenocarcinoma -> surgery: -suprastructure -> radiation therapy -infrastructure -> consider follow-up or radiation therapy for free-margin cancers or cancers that do not infiltrate the perineurium

zumab (up to 6 months), and the benefit of pembrolizumab outweighed its risks. Hyponatremia and elevated liver enzyme concentrations were the most frequent adverse effects of pembrolizumab, and no deaths related to pembrolizumab administration were recorded [19]. Among patients with HNSCC, the most common serious adverse effects of pembrolizumab included pneumonia (3.6%) and dyspnea (3.1%) [18]. Currently, the phase III KEYNOTE-040 study is further evaluating the efficacy of pembrolizumab.

Nivolumab is the newest FDA-approved biological therapy for HNCs. Nivolumab's mechanism of action resembles that of pembrolizumab [20]. In the phase III CheckMate-141 study, nivolumab reduced the risk of death by 30% compared to standard therapy, and the mean overall survival in patients treated with nivolumab was 7.5 months compared to 5.1 months in patients who received standard therapy [21].

The combination of cetuximab, platinum-based chemotherapy, and 5-FU followed by maintenance treatment with cetuximab, i.e., the EXTREME regimen, remains the first-line treatment for patients with R/M HNSCC because this regimen is associated with the greatest proportion of complete responses and the longest overall survival [22]. Patients who do not qualify for the EXTREME regimen can receive monoclonal antibodies that target immune checkpoint inhibitors as the sole treatment [12].

Tab. IX. Changes of treatment guidelines for melanomas of the mucous membranes.

NCCN GUIDELINES HEAD AND NECK CANCERS 2010	NCCN GUIDELINES HEAD AND NECK CANCERS 2017
Maxilloethmoidal complex T4b -> Clinical trials (preferred) or chemotherapy T4c -> Clinical trials (preferred) or palliative treatment	T4b-c -> Clinical trials (preferred) or chemotherapy or radiation therapy or palliative treatment (in T4c)
Oral cavity, pharynx, larynx T4b -> Clinical trials (preferred) or chemotherapy T4c -> Clinical trials (preferred) or palliative treatment	T4b -> Clinical trials (preferred) or radiation therapy and/or chemotherapy T4b-c -> Clinical trials (preferred) or chemotherapy or radiation therapy or palliative treatment (in T4c)

CONCLUSIONS

Updates of the NCCN guidelines for the treatment of HNCs are based on the long-term experience of many American oncology centers, basic research findings, clinical trials, and current knowledge. The motto of the NCCN guidelines is "the better you know and understand treatment algorithms, the easier it is to change them for individual patients". Only evidence-based medicine enables personalized treatment, which can be safely used outside the existing treatment schemes. In patients with HNCs, biological therapy is associated with lower toxicity and better quality of life.

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