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How comorbidities affect the surgical treatment planning in elderly patients with head and neck cancer?

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ABSTRACT

BACKGROUND. Head and neck cancer is the sixth leading cancer by incidence worldwide. Surgery and postoperative radiotherapy are the current standards in the treatment of head and neck cancer (HNC). Chemotherapy in combination with the listed methods is also used. However, the choice of a treatment sequence may be different for individual patients. Cancer patients are predominantly individuals aged 65 years and over, with a number of treated or untreated concomitant diseases. Therefore, comorbidities play a very significant role in treatment planning in this group of patients.

METHODS. The issue was explored in a retrospective study of medical records of 108 HNC patients hospitalized at the Department of Maxillofacial and Plastic Surgery, Medical

University of Bialystok. The study focused on patients older than 65 years old as they are most predisposed to co-existing diseases which can affect treatment planning. The data were analyzed by gender, age and presence of comorbidities as well as by lesion location, histopathology, cancer staging notation system (TNM), treatment methods.

RESULTS. Out of all cancer patients older than 65 years old, 44 were female and 64 were male at the average age of 75 and 78 years, respectively. The oldest patients were 88 years old (female) and 90 years old (male). Comorbidities were found in 62% of cases – 66% of women and 59.4% of men. The most frequent comorbidities were: hypertension – 41%, alcohol abuse – 17%, diabetes mellitus – 14%, hyperlipidemia – 9%, coronary heart disease – 6%, asthma – 4%, atrial fibrillation – 3% of patients. 97% of patients underwent surgery, but in 17 cases (16%) the treatment plan had to be altered due to the patients' general health. Only 3% of patients were disqualified from surgical treatment due to their general condition.

CONCLUSIONS: The choice of a treatment method in HNC patients should always be individualized. Comorbidities, in a severe, unregulated form may reduce treatment options or be a contraindication to standard therapy methods. Fortunately, in the majority of cases, the diversity of available surgical treatment modalities enables the selection of the most appropriate method for a particular patient on the basis of his/her general condition.

Key words: head and neck cancer, treatment, comorbidities

BACKGROUND At present, comorbidity is a common problem in patients treated at multidisciplinary hospitals. It is particularly prevalent in internal medicine departments, but also concerns cancer patients. Co-occurrence of multiple diseases has become the norm rather than the exception. Oncological patients form a specific group since they are predominantly individuals over 65 years old who have previously been exposed to

carcinogenic agents such as tobacco or alcohol. These are also considered risk factors for a number of internal diseases including cardiovascular, lung, liver and endocrine disorders as well as other cancers. Head and neck cancer (HNC) is the sixth cancer by incidence worldwide and accounts for 6% of all cancer cases. Each year 644,000 new cases are diagnosed, of which two-thirds occur in developing countries. Males are more predisposed - morbidity in this group reaches 9% while in females it stands at approximately 5%. Malignancies located in the head and neck region (upper aerodigestive tract) affect some of the individual's most essential functions including speech, communication, swallowing, eating, and appearance. They cause considerable anxiety and negatively impact on patients' quality of life. Various therapy methods are used to treat this type of cancer- either an appropriate single-modality method or multiple-modality treatment for each type of tumor is selected and implemented. The most approved management options for HNC patients are surgery, followed by radiotherapy. Chemotherapy as a single modality is rarely recommended in HNC, although it may be used as an induction therapy prior to surgery or in combination with radiotherapy (chemo radiotherapy). The 5-year patient survival rate ranges between 20% and 70% and prognosis depends on the early diagnosis, tumor location, local advancement, histopathological malignancy and existence of metastasis. The aim of this paper was to demonstrate how comorbidities influence the choice of a treatment method. ^[1,2,3]

METHODS

A retrospective study of the medical records of patients treated in the Department of Maxillofacial and Plastic Surgery, University Hospital of Bialystok, Poland, between January 2012 and December 2014 was performed. The study focused on patients older than 60 years old as they are most predisposed to some co-existing diseases which can affect treatment planning. In the period under investigation, 108 head and neck cancer patients were admitted to the Department, some of whom a number of times. Past medical history was obtained from all patients and their general health was assessed at the time of diagnosis by two physicians (a maxillofacial surgeon and an anesthesiologist) and noted in their medical records. Designated members of the study team summarized it retrospectively and performed statistical analyses (Statistica 9.0, using t-Student's test at a significance level of $p < 0.05$). The data analysis included the patients' general information (gender, age), presence of comorbidities, tumor location, cancer staging notation system (TNM), histopathology examination results and treatment modalities.

RESULTS

Out of all cancer patients older than 65 years old, 44 were female and 64 were male at the average age of 75 and 78 years, respectively. The oldest patients were an 88-year-old female and a 90-year-old male.

Comorbidity. Among patients included in the research, comorbidities were found in 62% of cases – 66% of women and 59.4% of men. The most frequent comorbidities were: hypertension – 41%, alcohol abuse – 17%, diabetes mellitus – 14%, hyperlipidemia – 9%, coronary heart disease – 6%, asthma – 4%, atrial fibrillation – 3% of patients. (TAB. 1).

TAB. 1 – the most frequent comorbidities among patients included in research

DISEASE	PERCENTAGE OF PATIENTS
hypertension	41%
alcohol abuse	17%
diabetes mellitus	14%
hyperlipidemia	9%
coronary heart disease	6%
asthma	4%
atrial fibrillation	3%

Comorbidities which occurred less frequently included hepatitis, overweight, dementia, depression, osteoarthritis, cataract, glaucoma, oesophageal reflux, psoriasis, chronic obstructive pulmonary disease (COPD), prostatic hypertrophy, thyroid nodular goiter, hypothyroidism, stomach ulcers, anemia, liver transplantation, emphysema. Tobacco smoking, a habit characteristic of this group of patients, also constituted a significant factor in

treatment planning since it would have affected healing or the possibility of metastasis. Almost 90% of the studied patients were addicted to nicotine (smoked more than 10 cigarettes per day) and did not stop smoking following cancer treatment.

Evaluation of the perioperative risk was based on the ASA (American Society of Anesthesiologists) physical status classification system. It is closely connected with comorbidities and is used by anesthesiologists to qualify patients for general anesthesia. ASA classification is presented in Table 2. The largest group of patients were classified as ASA 2 (52%) and ASA 3 (28%). Comorbidity and ASA classification both provide prognostic data assisting doctors in the decision-making process concerning patient management.

TAB.2 - ASA physical status classification system and percentage of patients included in each stage

Classification	Physical condition of the patient	Percentage of patients
ASA 1	Normally healthy	17%
ASA 2	Mild to moderate systemic disease, medically well-controlled	52%
ASA 3	Severe systemic disease which limits activity but is non-incapacitating	28%
ASA 4	Life-threatening, severe, incapacitating systemic disease	3%
ASA 5	Moribund with death expected within 24h, with or without surgery	0%

Location. The most frequent tumor locations were the floor of the mouth - 37 patients, which made up nearly 29% of all cases, and tongue – 29 patients, which constituted 22.5% of cases. Other locations are presented in Table 3.

TAB.3 – The most frequent tumor locations in patients included in research

Location	Percentage
Floor of the mouth	28.70%
Tongue	22.50%
Gingiva	17.10%
Cheek	9.30%
Lip	7.70%
Palate	7.00%
Pharynx	5.30%
Maxillary sinus	1.50%
Skin of the face	16.90%

Advancement. Tumor stage was defined on the basis of the clinical examination, radiological imaging and histopathological diagnosis. It was classified according to the criteria of the TNM classification of the UICC (Union Internationale Contre le Cancer) 2010. The most frequent tumor stages were T2 or T4, N0 or N1 and M0. Metastases were found in the lungs - 10 patients and liver – 1 patient. All statistical data are presented in Table 4.

TAB.4 – TNM classification with percentage of patients included in each stage

Stage	Percentage
T1	7%
T2	33%
T3	26%
T4	34%
N0	35%
N1	45%
N2	30%
M0	90%
M1	10%

TAB.5 - Differentiation stage of cancer in patients included in research

GRADE	PERCENTAGE
G1	23%
G2	63%
G3	14%
G4	0%

Histopathological examination. The most frequent type of cancer in the examined patients was squamous cell carcinoma – 78%. Other types of cancer included carcinoma adenoides cysticum – 3% and adenocarcinoma – 1.8%. The aforementioned percentage values refer to the mucosa of the oral cavity, pharynx and maxillary sinuses. Virtually all skin cancer cases were diagnosed as basal cell carcinoma (BCC), which constituted 16% of all cancer cases. Only 1 skin lesion was diagnosed as squamous cell carcinoma – 0.9% of cases.

In the evaluation of the differentiation stage of cancer, general grades recommended by the American Joint Commission on Cancer were used (grades G1-G4). The most common type of cancer was G2 – 63% of patients, G1- 23% and G3 - 14%. All results are presented in Table 5.

Treatment. Treatment plans were based on multidisciplinary case consultations and each plan was individualized. . 97% of patients underwent surgery, but in 17 cases (16%) the planned, comprehensive surgical treatment had to be altered due to the patients' poor general health and the associated increased risk of perioperative complications. . In 30% of patients who received surgical treatment free flaps were used for tissue reconstruction, in 44% - regional pedicled flaps were utilised, in 18% - a local tissue transfer and in 8% - a simple wound closure were used. 35% of patients (skin cancer (BCC) and T1-2N0 oral cancer patients)_did not require postoperative, multiple-modality oncological treatment. . 50% of cases were qualified for surgery and postoperative radiotherapy, 12% - underwent surgery and postoperative radio chemotherapy. Only 3% of patients were disqualified from surgical treatment due to their general condition and comorbidities (ASA 4). The ASA classification was not decisive as a number of factors were taken into consideration during treatment planning, e.g. tumor stage, its location, presence of metastasis, patient's age, general health

with co-existing medical problems and perioperative risk. All results concerning treatment methods in the studied patients are presented in Table 6 and Table 7.

TAB.6 – Treatment methods in patients included in research

METHOD OF TREATMENT	PERCENTAGE
Surgery	35%
Surgery and radiotherapy	50%
Surgery and chemo radiotherapy	12%
Disqualified from surgical treatment	3%

TAB.7 – Methods of reconstruction in patients qualified for surgical treatment

METHOD OF RECONSTRUCTION	PERCENTAGE
free flap	30%
regional pedicled flap	44%
local tissue transfer	18%
simple closure	8%

DISCUSSION

The study demonstrated that the majority of HNC patients were over 65 years of age. Research by other authors has also revealed that cancer prevalence increases progressively with age. It is predicted that 20% of the European population will be aged 65 and over by the year 2030 and that, despite falling cancer mortality rates, cancer incidence will increase due to a rise in the number of older people and their age-related susceptibility to the disease .^[4] The incidence of comorbidities such as diabetes mellitus and hypertension, partly associated with age, is also projected to increase dramatically. It is estimated that by the year 2030 the number of patients with hypertension will rise from 130.2 to 216.8 million worldwide, and the population of diabetics will soar from 195 to 360 million (4.5% of the global population).^[5,6]

Despite the fact that older patients constitute a very heterogenic group and their chronological age does not always correspond to their physiological status, the majority of

them need individualized treatment plans. In every case physicians have to obtain information on the patient's physiological and functional capacity in order to be able to provide safe and effective treatment recommendations.^[7,8] Therefore, it is vitally important for doctors to understand interactions between co-occurring conditions while preparing management plans for geriatric patients. The crucial issues of comorbidity measurement, interventions, and future research were discussed in a debate between the Cancer and Ageing Research Group, the National Cancer Institute and the National Institute on Aging in May 2015^[9,10,11].

Out of the total number of patients studied, 62% suffered from a number of co-existing diseases. The most frequent were hypertension, diabetes mellitus, coronary heart disease and alcohol abuse. A significant finding of our research related to the fact that nearly 90% of patients smoked, which –is considered a primary head and neck cancer risk factor in elderly people. The aforementioned comorbidities have also been repeatedly mentioned in the available literature.^[1,2,3,4] It is estimated that the prevalence of comorbidity varies from 0.4% to 90% among cancer patients. The figure depends on the selected method of comorbidity measurement, study population and cancer type.^[12,13]

To evaluate the significance of comorbidities and their influence on the treatment plan, we used the ASA physical status classification system. It defines severity of comorbidities, which is directly connected with the patient's general physical condition. Moreover, it can be a predictor of intraoperative and postoperative complications including prolonged respiratory therapy, respiratory failure, electrolyte imbalance, heart dysfunction.^[14,15] We believe that the ASA scale has some limitations as it does not address other prognostic disorders such as psychiatric diseases or previous radiotherapy, which are also important in patient management planning. However, it is simple and widely used and therefore conducting a retrospective study based on this classification was possible. None of the authors of similar papers have used the ASA classification. Different indexes were chosen, e.g. ACE-27, Charlson Comorbidity Index, Eastern Cooperative Oncology Group Scale Kaplan Feinstein Classification, Activities of Daily Living or Instrumental Activities of Daily Living.^[1,2,3,4,14,16,17,18] All those methods have certain limitations as well. We have not found a reliable prognostic factor or index which alone would enable us to qualify patients for a particular treatment modality.

Apart from comorbidities, our study explored the significant impact of the stage of tumor advancement on treatment choice. In the studied group of patients, stage III and IV

tumors (T3 and T4) were more frequent than less advanced tumors (60%). Metastases to local lymph nodes were often documented - in 65% of patients (N1 - 45%, N2-20%), while distant metastases occurred only in 10%. The most common organs where HNC had metastasized were lungs (10 cases) and liver (1 case). As stated in the literature, locally advanced tumors (T3 and T4 according to the TNM classification) occur more often in elderly patients and the incidence of metastasis to regional lymph nodes is relatively infrequent - observed in only 10% of cases at the time of diagnosis.. Furthermore, approximately two-thirds of HNC patients revealed only locally advanced disease.^[4] Histologically, the most frequent type of cancer in the researched patients was squamous cell carcinoma in the case of oral mucosa and basal cell carcinoma in the case of skin. The largest group of patients had G2 type of cancer, while the least frequent type was G3. G4 type of cancer was not observed. Similar results have been published in the available literature. It is estimated that well differentiated tumors are more specific to older patients.^[22,23,24]

Treatment in head and neck oncology is heterogeneous. It is connected with the size of the tumor, its location, histological type, presence of metastasis, patients' general condition and comorbidities. Three therapy methods are generally approved: surgery, radiotherapy and chemotherapy. The current treatment of choice for locally advanced tumors is major surgery followed by radiotherapy. Chemotherapy is implemented as part of multiple-modality treatment or used in palliative care.

A surgical procedure based on resection and reconstruction is usually the most appropriate for HNC and should be preferred if the primary tumor can be resected with clear margins without causing functional problems. A number of different reconstructive methods ranging from relatively simple to very complicated and demanding for both the surgeon and the patient have been described in the literature. The gamut of reconstructive methods, classified as the "reconstructive ladder", is presented in Table 8. The choice of treatment should start with the simplest method and progress to more sophisticated modalities until an appropriate technique is selected.^[20]

TAB.8 – Reconstructive ladder

Stage	Method of reconstruction
5	Free tissue transfer
4	Regional tissue transfer
3	Local tissue transfer, tissue expansion
2	Skin graft
1	Simple closure

Simple wound closures, skin grafts or local flaps can be used for the reconstruction of soft tissue after the resection of less advanced tumors. These methods are simpler, cause less patient discomfort and provide a satisfactory aesthetic result. However, when a larger resection is needed, these methods may be insufficient. In the case of advanced tumors (T3-T4), the most comprehensive method of reconstruction should always be chosen including distant vascularized flaps with microsurgical anastomoses. It provides the best functional restoration and aesthetic effect, although surgery duration is comparatively long (10-12 hours). However, in some cases, the patient's poor general condition precludes large reconstructive surgery. In such situations, a simpler method has to be adopted. ^[19]

According to our research, 97 % of patients were qualified for surgical treatment, but 16% of them were subsequently operated on using suboptimal treatment methods. Considering tumor related factors such as its location, advancement and histopathological type, the most appropriate method of surgical reconstruction should have been the free flap. However, due to the patients' general condition and unregulated comorbidities some regional flaps or local tissue plastic surgery procedures were implemented. According to literature reports, prolonged surgery duration (exceeding 10 hours) is considered a predictive factor for the development of postoperative complications. ^[4,21] As stated in the literature, the treatment of HNC patients, especially geriatric patients suffering from numerous comorbidities, sometimes requires compromises such as the adoption of a suboptimal treatment scheme which may be better tolerated by the patient during surgery than standard methods. ^[4] Clinicians should always consider the risk-benefit ratio in patient management planning. Therefore, if possible, all diseases such as severe cardiovascular disorders, sustained hypertension, acute liver and renal dysfunction, anemia, uncontrolled diabetes, airway inflammatory disease, acute or severe asthma, or bleeding disorders should be regulated. This would minimize the risk of perioperative and postoperative complications. ^[15]

In our study of 108 cases, 3 patients were disqualified from surgical treatment due to their poor general condition. The first patient, an 86-year-old female was disqualified due to her age, rheumatic fever, advanced dementia and a few episodes of syncope which occurred during hospitalization. The second patient, an 83-year-old male with concomitant emphysema and disturbances of consciousness, did not qualify for surgery due to an increased risk of perioperative mortality associated with general anesthesia. The last patient, a 69-year-old male was disqualified due to severe, unregulated cardiovascular disease and myocardial infarction which he had suffered two months prior to cancer diagnosis. The aforementioned patients were classified as ASA IV patients.

Authors of articles similar to ours emphasize the importance of comorbidity evaluation in cancer patients. Wang et. al. suggests that the presence of concurrent diseases not only has an unquestionable, direct impact on patient survival, but may also affect it indirectly by influencing treatment choice. It has been indicated that although age itself may not always disqualify patients from receiving the most appropriate, comprehensive treatment, the presence of comorbidities associated with advanced age may result in a selection of a less aggressive, simpler treatment modality. [3] Sadat et. al. specifies that the presence of an additional disease without a measure of its severity is not a reliable predictor of the functional effect of the illness. [1] Patnaik et al. in their paper demonstrated that comorbidities can be as important as staging in predicting breast cancer survival. The survival rates of patients with a number of comorbid conditions diagnosed with early-stage breast cancer were similar to or worse than those of patients with no comorbidities diagnosed with later-stage tumors. [14]

The issue of the impact of comorbidity on the survival of HNC patients has been widely researched. However, there is a paucity of published studies which have directly investigated comorbidity and the general condition of head and neck cancer patients, and their impact on the selected treatment modality.

CONCLUSIONS

The patient's age and presence of comorbidities are not the sole determinants of treatment planning of head and neck cancer patients. Comorbidities may influence the choice of a treatment modality but only in their severe, unregulated form, in which case they may reduce treatment possibilities or be a contraindication to the utilisation of standard therapy methods. This issue is acquiring significance as the number of patients with concomitant diseases is projected to grow in the coming decades. Therefore, close cooperation between

surgeons and general practitioners, cardiologists or endocrinologists is of utmost importance. Fortunately, in the majority of cases, the diversity of available surgical treatment modalities enables the selection of the most appropriate method for a particular patient on the basis of their general condition.

DECLARATIONS

Ethical approval and consent to participate - Not applicable (the research was based on the retrospective analysis of medical documentation owned by the Department of Maxillofacial and Plastic Surgery in Bialystok, in was not clinical trial or experiment, it did not involve human participants).

Availability of data and materials - All data generated or analyzed during this study are included in this published article (and its supplementary information files).

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

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