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Effects of Neoadjuvant Therapy After the Initial Assessment of Operability in Patients with Borderline Operable and Inoperable Stage IIIA Non-small Lung Cancer

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ABSTRACT

Introduction: Lung cancer is a neoplasm with the highest mortality rate in the world. The role of neoadjuvant therapy in patients with initially assessed borderline operable or inoperable lung cancer is to improve survival by downstaging the tumor and allowing surgical resection, as well as the potential treatment of micrometastatic disease. **Aim:** Establishing the justification and efficacy of neoadjuvant therapy after the initial assessment of operability in patients with borderline operable and inoperable histopathologically verified stage IIIA non-small cell lung cancer. **Methods:** The retrospective study included 65 patients with initially assessed stage IIIA lung cancer, who underwent neoadjuvant therapy. After the cycles of neoadjuvant therapy, 19 patients who achieved the regression of the tumor underwent surgery. We analyzed the histological type of the tumor, extent, and prevalence of surgical resection, the status of regional lymph nodes, and the achieved R status. **Results:** Of the total number of patients who underwent neoadjuvant therapy, after reevaluation of the disease, 19 patients (19/65, 29.23% of cases) achieved a clinical response, i.e. tumor downstaging. Of 19 patients who underwent surgery, 16 patients underwent surgical resection, while three patients underwent surgical exploration. The largest number of patients had N0 and N1 status (six patients each). R0 status was achieved in 14 patients (14/16, 87.5% of cases), while R1 in the remaining two. One patient had a fatal outcome. **Conclusion:** Neoadjuvant therapy plays an important role in the treatment of initially assessed borderline operable or inoperable lung cancers. By downstaging the tumor, it allows surgical resection and potential treatment of micrometastatic disease.

Keywords: lung cancer, neoadjuvant therapy, lobectomy, inoperable cancer, pulmectomy.

1. INTRODUCTION

Lung cancer is the third most commonly diagnosed cancer in Europe (470.000 newly diagnosed cases per year, i.e. 12% of all cancer cases), and at the same time has the highest mortality rate (388.000 deaths per year, i.e. 20% of all cancer deaths). In the United States, lung cancer is the most commonly diagnosed cancer (11.6% of all cancer cases per year), and it is cancer with the highest mortality rate (18.4% of all cancer deaths) (1). The most common treatment options include surgery, radiotherapy, and chemotherapy. Treatment options may vary depending on the type of tumor, the stage of the disease, as well as the patient's general condition (2). Staging of the tumor is based on the Tumor, Nodus, Metastasis (TNM) International Classification of Malignant Tumors.

Surgical resection is reserved primarily for early stages of non-small-cell lung carcinoma (NSCLC), i.e. I and II, either as monotherapy or as part of a multimodality approach, with adjuvant (postoperative) therapy.

To improve prognosis and survival rates, various therapeutic modalities in the form of adjuvant and neoadjuvant chemotherapy have been introduced (3). "Neoadjuvant", "protoadjuvant" or, according to the new nomenclature, "induction" therapy is defined as a cytoreductive therapy that precedes the definitive locoregional treatment, i.e. surgical resection. It is considered in patients with stage IIIA (T1-3 N2) NSCLC and certain patients with histopathologically verified stage IIIB (T4 or N3) NSCLC. The main goal of this

type of therapy is to improve survival by "downstaging" the tumor, therefore allowing surgical resection in patients with initially assessed borderline operable or inoperable lung cancer by acting on the primary tumor, mediastinal lymph nodes, and possibly micrometastases. According to numerous studies, neoadjuvant therapy combined with surgical treatment has a significant effect on improving patient survival, by reducing the relative risk of death by 13%, compared to those patients treated with surgery alone (4). Early clinical trials of neoadjuvant immunotherapy via so-called immune-checkpoint inhibitors in monotherapy as well as in combination with chemotherapy, as well as neoadjuvant molecular therapy studies show promising results (5).

Clinical TNM (cTNM) is based on the clinical staging of the tumor. According to the stage, physicians determine different treatment modalities for each patient. The most widely accepted criteria for assessing the involvement of mediastinal lymph nodes in patients with lung cancer is the diameter of the shorter axis of the lymph node, which should be over 10 mm on transverse computed tomography (CT) scans. Lymph nodes smaller than 10 mm have a low probability, 10-15 mm a moderate probability, while lymph nodes over 15 mm have a high probability of tumor involvement. Cytopathological and histopathological analysis confirm or deny the diagnosis of lung cancer.

2. AIM

This study aims to establish the justification and efficacy of neoadjuvant therapy after the initial assessment of operability in patients with borderline operable and inoperable histopathologically verified stage IIIA non-small cell lung cancer.

3. PATIENTS AND METHODS

Clinical stage classification is based on the patient's medical history, physical examination, and imaging (chest X-ray (CXR), CT of the chest, ultrasound of the abdomen, bronchoscopic evaluation of the tumor) done before initiation of treatment.

We conducted a retrospective study of 65 patients who underwent neoadjuvant chemotherapy from January 2015 to December 2019 at the Clinic of Thoracic Surgery and the Clinic for Lung Diseases of the Clinical Center University of Sarajevo. The inclusion criteria and neoadjuvant therapy include patients with a previously histologically or cytologically diagnosed stage IIIA NSCLC (T1-3 N2) and selected patients with IIIB NSCLC (T4 or N3), i.e. borderline operable or inoperable cases of lung cancer. The initial stage assessment was based on cTNM before and ycTNM during and after neoadjuvant therapy.

We analyzed the following clinical and pathological characteristics of patients included in our study:

- Demographic characteristics (gender, age);
- Histological type of cancer, according to the World Health Organization (WHO) guidelines;
- Extent of surgical resection;
- Clinical staging before neoadjuvant therapy (cTNM);
- Clinical staging after the administration of neoadjuvant therapy (ycTNM);
- Pathological staging (pTNM);
- Lymph node status (N status);
- Presence of residual tumor (R0, R1, and R2).

4. RESULTS

From January 2015 to December 2019 a total of 65 patients with diagnosed stages IIIA or IIIB NSCLC underwent neoadjuvant chemotherapy at the Clinic of Thoracic Surgery and the Clinic for Lung Diseases of the Clinical Center University of Sarajevo. The mean age of the patients was 62.03 years, and there were 55 males and 10 females. The male-to-female ratio was 5.5:1.

Of the total number of patients who underwent neoadjuvant therapy, after reevaluation of the disease, 19 of them (19/65, 29.23% of cases) achieved a clinical response, i.e. tumor downstaging. Of 19 patients who underwent surgery, 16 patients underwent surgical resection, while three patients underwent surgical exploration. Types of treatment in all 65 patients, who previously underwent neoadjuvant therapy, are shown in Chart 1.

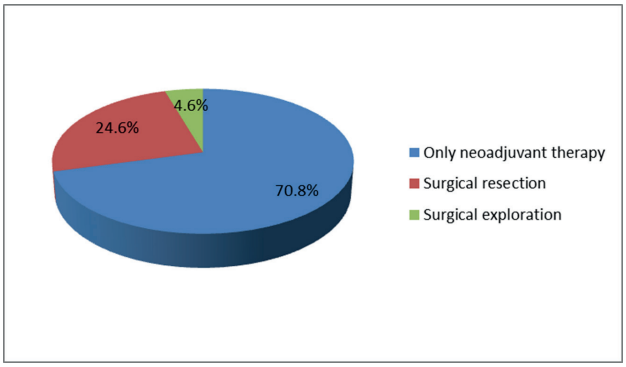

Chart 1. Types of treatment in patients with borderline operable and inoperable lung cancer after neoadjuvant therapy

The histological type of cancer in all patients treated with neoadjuvant therapy is shown in Chart 2.

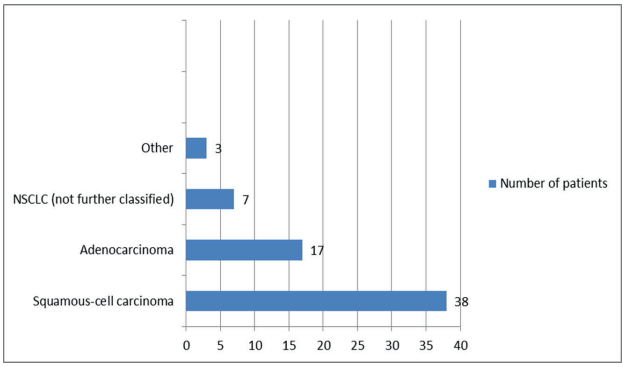

Chart 2. Distribution of all patients who underwent neoadjuvant therapy according to the histological type of cancer

Chart 3 depicts the histological type of cancer in patients who underwent surgery.

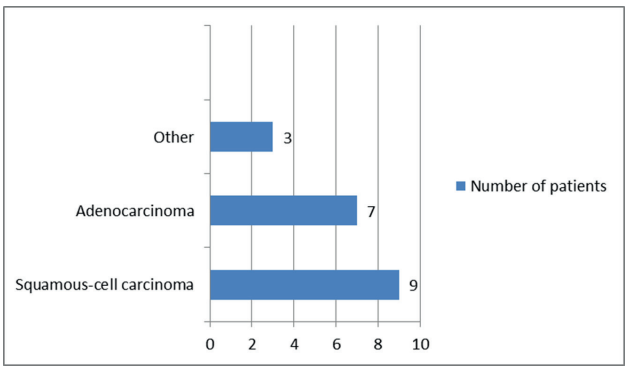

Chart 3. Distribution of patients who underwent surgery according to the histological type of cancer

Of the total number of patients who underwent surgery, we performed anatomical resection in 15 of them, non-anatomical (atypical or wedge) resection in one patient, and surgical exploration in the remaining three patients, as shown in Chart 4.

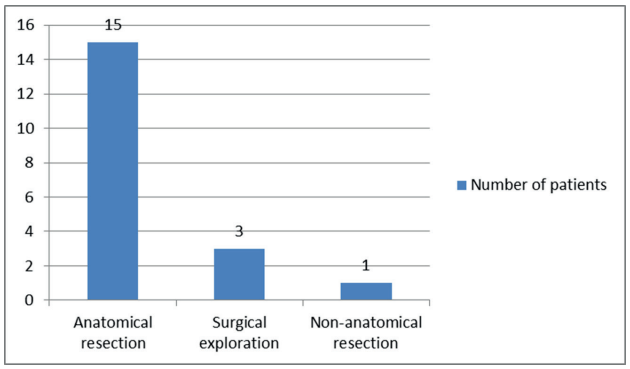

Chart 4. The extent of surgical resection in patients with tumor downstaging after neoadjuvant therapy

Regarding the type of surgical procedure, the most common were right pulmectomy and left lower lobectomy, which was performed in eight patients (four patients each). This is followed by left pulmectomy and right upper lobectomy in six patients (three patients each), and middle lobectomy, atypical (wedge) resection of the right upper lobe, and right upper bilobectomy in one patient each. In three patients with intraoperatively proven unresectable tumors, we performed surgical exploration. Another treatment option was offered for these patients.

Chart 5. shows different types of surgical procedures and their distribution among patients.

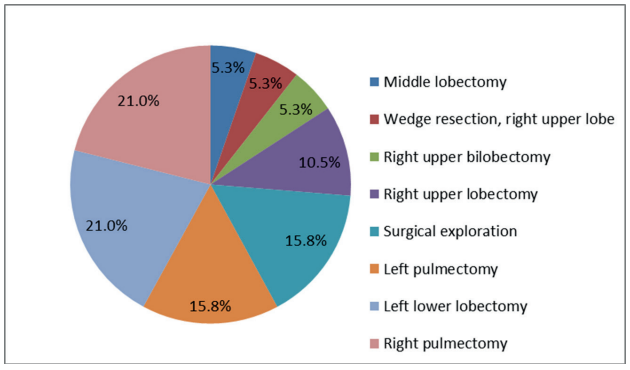

Chart 5. Types of surgical procedures and their distribution among patients who previously underwent neoadjuvant therapy

The definitive histopathological finding after surgery revealed the regional lymph node status, according to the TNM classification. Six patients (6/19, 31.57% of cases) who underwent surgical resection did not have cancer cells present within lymph nodes (N0). The same number of patients had metastases in unilateral peribronchial and/or unilateral hilar lymph nodes, as well as positive intrapulmonary lymph nodes (N1), while in two patients (2/19, 10.52% of cases) metastases in unilateral mediastinal and or subcarinal lymph nodes (N2) were verified. The status of regional lymph nodes was not determined in the remaining four patients and they were excluded from the analysis of lymph node status. Three of these patients underwent surgical exploration due to an intraoperatively proven inoperable tumor and one patient underwent atypical resection. The relationship between the regional lymph node status, the diagnosis of lung cancer, and the extent of surgical resection are shown in Table 1.

Diagnosis	The extent of surgical resection	Lymph node status
Squamous-cell carcinoma	Middle lobectomy	Nx
Squamous-cell carcinoma	Left lower lobectomy	N0
Squamous-cell carcinoma	Left pulmectomy	N0
Squamous-cell carcinoma	Right upper lobectomy	N0
Adenocarcinoma	Right upper lobectomy	N0
Adenocarcinoma	Left lower lobectomy	N0
Adenocarcinoma	Right pulmectomy	N0
Squamous-cell carcinoma	Left pulmectomy	N1
Squamous-cell carcinoma	Right pulmectomy	N1
Squamous-cell carcinoma	Left lower lobectomy	N1
Adenocarcinoma	Right upper bilobectomy	N1a
Squamous-cell carcinoma	Right pulmectomy	N1b
Squamous-cell carcinoma	Left lower lobectomy	N1b
NSCLC (not further classified)	Right pulmectomy	N2
Adenocarcinoma	Left pulmectomy	N2a2

Table 1. The relationship between the diagnosis of lung cancer, the extent of surgical resection, and the regional lymph node status

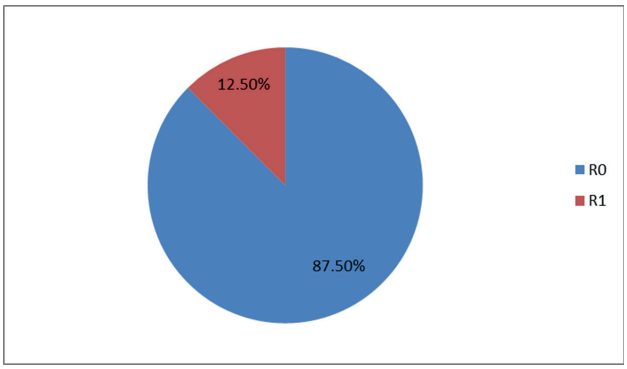

Chart 6. The distribution of R status among patients who underwent surgical resection

R status was determined in all patients who underwent surgical resection. A total of 14 patients (14/16, 87.5% of

cases) did not have residual cancer cells at the primary tumor site (R0), while the two remaining patients (2/16, 12.5% of cases) had a microscopic residual tumor (2/16).

Chart 6. depicts the distribution of R status among patients who underwent surgical resection.

5. DISCUSSION

The use of neoadjuvant therapy in patients with stage IIIA NSCLC is likely to reduce the tumor size and can make patients candidates for surgical resection (tumor downstaging). In our study, we tried to determine the effectiveness of neoadjuvant therapy. Neoadjuvant therapy can also treat underlying micrometastatic disease.

In their prospective phase III, randomized study, Rosell et al. demonstrated that the use of neoadjuvant therapy before surgery significantly improved survival rates compared to surgery alone (21-22 months and 10-14 months) in patients with stage IIIA lung cancer (6). The important role of neoadjuvant therapy in the treatment of borderline operable and inoperable patients with lung cancer was confirmed by a large retrospective study, which included over 11.000 patients with histopathologically verified stage IIIA-N2 lung cancer. The authors of this study demonstrated significantly better survival rates among the patients who underwent neoadjuvant therapy before surgical treatment (7). Tumor downstaging can be observed in 40–60% of patients who underwent neoadjuvant therapy, while a complete response is achieved in 5–10% of patients. Surgery is possible in about half of the patients, who were initially assessed as inoperable and underwent neoadjuvant therapy before the surgical treatment. In our study, 30% of patients were eligible for surgery, which could be explained by deficiencies in the selection of patients and cTNM, but also in the ycTNM. It is widely believed that surgical treatment is justified only with the evidence of clear regression at the level of the primary tumor and mediastinum.

Based on our previous experience, the smallest possible extent of resection should be performed. In patients with preoperatively confirmed N2 involvement, surgical treatment is recommended: a) in patients in whom thoracotomy reveals unexpected N2 involvement, but only if complete resection is possible; adjuvant chemotherapy should be included in the treatment, b) in patients in whom neoadjuvant therapy has led to a clear response at the level of the mediastinum, and only if complete resection is possible.

There are also studies, as well as meta-analyses, that have shown only a marginal benefit of neoadjuvant chemotherapy, with no statistically significant longer survival rates associated with this therapy. Comparing the assessment of tumor staging after the course of neoadjuvant therapy based on the RECIST guidelines and the pathological stage based on the histopathological examination of the tumor specimen, we notice that more patients had a pathologically (yp) lower stage of the disease than clinically estimated (yc).

We compared the clinical stages of the disease before and after the course of neoadjuvant therapy. Some regression of the tumor, i.e. tumor downstaging has been observed. In 70.77% of patients, the tumor remained in the same clinical stage, while in 29.23% of patients tumor downstaging was observed. According to RECIST guidelines, six patients (6/19, 31.57% of cases) with N0 lymph node status had a complete response to neoadjuvant chemotherapy. Neoadjuvant therapy allows a surgical treatment to a significant number of patients with less extensive resection of the lung parenchyma, early treatment of micrometastases, providing information on tumor chemosensitivity, but also increasing the risk of postoperative complications.

Albain et al. investigated a correlation between improved survival rates and the group of patients who underwent lobectomy after the course of neoadjuvant therapy, compared to patients treated with chemoradiotherapy alone (36 % and 18%; p = 0.002) (8). In our research, seven patients underwent lobectomy after a previous course of neoadjuvant therapy, with all of them having an uneventful postoperative course. According to the same research, the benefit of neoadjuvant therapy in the group of patients treated with pulmectomy is questionable. Pulmectomy was a surgical procedure performed in seven patients in our study (four patients underwent right pulmectomy and three left pulmectomy). All these patients were discharged from our clinic without complications. In our study, radical surgical treatment (R0) was performed in 87.5% of patients after the course of neoadjuvant therapy. No fatal outcomes were reported. Large meta-analyses have shown that certain variables such as the type of chemotherapy regimen, the number of chemotherapeutic agents in the regimen, and even the type of chemotherapy agent (cisplatin or carboplatin) do not significantly affect survival outcome. Age, gender, histopathological type of tumor (squamous versus nonsquamous), the Karnofsky Performance Status Scale (0 vs. 1 vs. 2+), and numbers of cycles of chemotherapy also did not significantly affect the benefit of neoadjuvant therapy in improving patients' overall survival rates (10).

6. CONCLUSION

- Induction or neoadjuvant therapy plays an important role in the treatment of initially assessed borderline operable or inoperable lung cancers, as it allows surgical resection and potential treatment of micrometastatic disease by tumor downstaging.
- Neoadjuvant therapy in selected cases of advanced lung cancer is a significant additional therapy, in terms of increasing the number of patients who can undergo radical surgical treatment, without significantly increasing postoperative complications, and helping improve survival rates of patients with locally advanced lung cancer.

- **Patient Consent Statement**: The first author confirms that patients consent to enroll in the study was obtained. The authors certify that they have obtained all appropriate patient consent.
- **Author contribution**: I.P.: concept and design, analysis and interpretation of data, drafting the article, final approval of the version to be published. I.P. and AAP: acquisition of data, drafting the article, final

approval of the version to be published. I.P,, S.M., A.H., A.P., K.K., K.G., O.C., and M.D. : concept and design, revising the article critically for important intellectual content, final approval of the version to be published. A.A.H.: analysis and interpretation of data, drafting the article, final approval of the version to be published. Final proofreading was made by the first author.

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