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REVIEW ARTICLE

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# Optimization of diagnostic and therapeutic management in patients with stage III non-small cell lung cancer — experience of the centers in Poznań

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## ABSTRACT

Lung cancer is one of the most frequently diagnosed malignancies, with one of the worst prognoses. Non-small cell lung cancer (NSCLC) is the dominant histological type, accounting for 85% of cases. In Poland, in more than one-third of patients, NSCLC is diagnosed at stage III. One of the most effective methods of radical treatment in such cases is concurrent radiochemotherapy. However, in Poland the percentage of patients eligible for this type of therapy is quite low, due to delayed diagnosis, lack of reference centers, long qualification process for treatment, and ineffective treatment organization. This article discusses the optimization of therapeutic management in patients with stage III NSCLC based on the experience of centers in Poznań (the Greater Poland Cancer Center and Greater Poland Center for Pulmonology and Thoracic Surgery). Some modifications include introduction of a surgery qualification form, urgent early evaluation using combined positron emission tomography (PET)/computed tomography (CT) and invasive mediastinum evaluation, and initial qualification for radiochemotherapy (with the setting of dates) already during diagnostics. These activities led to the multiplication of the number of patients qualified for concurrent radiochemotherapy.

**Key words**: non-small cell lung cancer, radiochemotherapy, concurrent radiochemotherapy, sequential radiochemotherapy, multidisciplinary team, durvalumab

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## Introduction

Lung cancer is one of the most frequently diagnosed malignant neoplasms in Poland and the leading cause of cancer-related deaths in both sexes [1]. More than 20000 lung cancer cases are diagnosed annually, with non-small cell lung cancer (NSCLC) being the most common subtype (approximately 85%) [2, 3].

In Poland, in approximately 35% of patients, NSCLC is diagnosed at stage III (in most cases this is an inoperable stage), and this percentage is higher than in some countries [4, 5]. According to the 2016 data from

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the American Cancer Society, the 5-year survival rate of patients with NSCLC in stages IIIA and IIIB was 14% and 5%, respectively [6].

According to the recommendations for chest neoplasms treatment issued by the Polish Society of Clinical Oncology, in patients with stage III NSCLC ineligible for surgery, concurrent (cCRT) or sequential chemoradiotherapy (sCRT), chemotherapy, or radiation therapy should be used. In the case of cCRT, the Polish guidelines recommend the use of consolidation treatment with durvalumab for 12 months [4]. The National Comprehensive Cancer Network (NCCN) guidelines recommend that patients with inoperable stage III NSCLC should be treated with cCRT with consolidation therapy with durvalumab [7]. Although it is one of the most effective methods of radical treatment, in Poland the percentage of patients eligible for this treatment is quite low [8]. By comparison, in the United States and the United Kingdom, approximately 50% of patients with stage III NSCLC receive cCRT [9, 10].

There is a possibility of increasing the cCRT use in Polish centers, as evidenced by data from Poznań centers — the Greater Poland Cancer Center (WCO, Wielkopolskie Centrum Onkologii) and the Wielkopolska Center of Pulmonology and Thoracic Surgery (WCPiT, Wielkopolskie Centrum Pulmonologii i Torakochirurgii). The solutions implemented by WCO and WCPiT contributed to a significant increase in the number of patients qualified for cCRT (from 12 in both 2018 and 2019 and 2 in the first half of 2020 to 30 in 2021) and consolidation therapy (from 1 in 2020 to 12 in 2021). This article aims to discuss the methods of optimizing the management of patients with stage III NSCLC based on the experience of the WCO and WCPiT.

## Treatment of stage III NSCLC

### Qualification for surgical treatment of stage III NSCLC

The most important factors in qualifying patients for surgical treatment include the disease stage, histological type, general performance status (PS), and the presence of serious comorbidities [11]. Radical surgery may be considered for T3/T4 and N0/N1 tumors. Patients with N2 disease constitute a diverse group, requiring an individual treatment approach. In such cases, there is a very important role of the multidisciplinary team (thoracic surgeon, pneumonologist, medical oncologist, radiation oncologistradiation oncologist, and radiologist), which classifies the tumors into a group of potentially resectable, potentially resectable with possible incomplete resection, or inoperative [12]. Surgical treatment may be considered in patients with single metastases in mediastinal lymph nodes and pathologically proved complete mediastinal lymph nodes response following induction treatment, usually including chemotherapy or radiochemotherapy [4, 13]. The use of induction therapy facilitates or enables complete resection. A meta-analysis by Guo et al. [14] showed that the use of preoperative radiochemotherapy in patients with stage III NSCLC is associated with better local disease control and tumor shrinkage with complete pathological response compared with chemotherapy. However, no prolongation of progression-free survival or increase in 5-year survival rate was observed. On the other hand, the use of postoperative chemotherapy (with or without radiotherapy) significantly extends overall survival; chemotherapy is recommended in patients in good PS, without serious comorbidities, and with complete recovery after pulmonary resection [4].

During surgery planning in patients with NSCLC with limited N2 disease, it is crucial to perform staging using minimally-invasive methods. The European Society of Thoracic Surgeons (ESTS) guidelines regarding the pre-operative mediastinal lymph nodes assessment recommend that computed tomography (CT), positron emission tomography (PET), or combined PET-CT should be performed first. Patients with no distant metastases (M0) and lymph node involvement (N0) are eligible for resection. In patients with N1 disease, a centrally located tumor or tumor larger than 3 centimeters in diameter, invasive examinations should be performed including evaluation and biopsy of mediastinal lymph nodes during endobronchial ultrasound (EBUS), esophagal ultrasonography (EUS), or video-assisted mediastinoscopy (VAM) due to a significantly higher risk of radiologically silent N2 disease. If the case of N2 disease suspected in radiological examinations, the aforementioned invasive diagnostic methods are the standard of care. In both situations, surgical treatment is used after exclusion of N2 disease [4, 12].

In a survey on the management of patients with N2 disease conducted by the NCCN, approximately 90% of respondents declared that radical surgery should be considered in the case of involvement of one lymph node smaller than 3 centimeters in diameter, while almost 48% of physicians declared that radical surgery should be considered in the case of N2 involvement of more than one lymph node if none of them exceeds 3 centimeters. In addition, 80% of physicians performed an initial assessment of the mediastinal lymph node with the use of EBUS/EUS [7].

The data regarding the number of NSCLC patients undergoing lung resection in WCPiT in 2016–2019 indicate that each year about 20% of patients had stage IIIA cancer, while in half of them, IIIAN2 tumor was diagnosed postoperatively (10%). By comparison, according to the nationwide data from the National Lung Cancer Database, stage IIIA NSCLC accounted for approximately 14% of all operated tumors [15].

## Radiochemotherapy

A combination of radiotherapy with chemotherapy is more effective than radiation alone, and cCRT is associated with better outcomes than sequential treatment [4, 16]. In patients with inoperable stage III NSCLC in good general condition, with a slight decrease in body weight, adequate respiratory capacity, and limited tumor burden, the use of cCRT is recommended. In the case of contraindications to cCRT, the use of sCRT should be considered [12].

Radiation therapy alone in patients with locally advanced tumors is associated with poor outcomes due to the high risk of distant metastases. Chemotherapy improves the local effectiveness of radiotherapy through the radiosensitizing effect (it mainly concerns platinum derivatives) and reduces the risk of blood-borne dissemination [16]. A meta-analysis of phase III trials showed that combined radiotherapy and chemotherapy reduce the risk of death by 13% and increase the 2-year survival rate by 4% compared to radiation alone [17]. Sequential radiochemotherapy also led to an increase in the 5-year overall survival rate from about 5% to 10% compared to radiotherapy alone, and concurrent use of both methods increases it to about 15% [16, 18]. Compared to sCRT, cCRT reduces the risk of death by 14% after two years and significantly reduces the risk of local progression [19, 20].

cCRT is associated with several times higher risk of acute (≥ grade 3) esophagitis and slightly more intense pneumo- and myelotoxicity than sCRT. Concurrent radiochemotherapy should, therefore, only be used in specialized centers capable of treating possible complications [21].

Patients eligible for radiochemotherapy (cCRT and sCRT) are in good performance status (ECOG 0–1), without significant weight loss (up to 10% of the ideal body weight during 3 preceding months), with limited tumor mass, adequate respiratory capacity, and without significant comorbidities. Patients over 70 years of age in a very good PS qualify for sCRT [4, 16, 22]. There are reports of concurrent therapy benefits in the elderly, but the evidence is still limited [23]. Age is not considered to be an absolute contraindication for cCRT, but a comprehensive geriatric evaluation should be performed, including the risk based on medical comorbidities and the patient's overall functioning.

Regimens of chemotherapy used as part of cCRT include:

— cisplatin at a dose of 75–100 mg/m$^2$ (day 1) with vinorelbine at a dose of 25–30 mg/m$^2$ (days 1 and 8) every 21 days;
— cisplatin at a dose of 75–100 mg/m$^2$ (day 1) with etoposide at a dose of 100–120 mg/m$^2$ (days 1, 2, and 3) every 21 days.

Sequential chemoradiotherapy can include either one of the above regimens or cisplatin in combination with docetaxel (75 mg/m$^2$ — day 1), paclitaxel (200 mg/m$^2$ — day 1) or gemcitabine (1000–1250 mg/m$^2$ — day 1 and 8). If cisplatin is contraindicated, carboplatin may be used (AUC 6 — day 1). Subsequent cycles of chemotherapy are administered every 21 days [4].

In NSCLC with other than predominantly squamous cell histology, pemetrexed (500 mg/m$^2$) based chemotherapy with either cisplatin (75 mg/m$^2$) or carboplatin (AUC 5) can be used [24–26].

In radical concurrent or sequentially radiochemotherapy, conventionally fractionated (1.8–2 Gy per day), conformal radiation at a total dose of 60–66 Gy is used [4, 12]. Irradiated area should include the primary tumor and the affected hilar and mediastinal lymph nodes. The development in radiotherapy and the possibility of using modern techniques allow for more precise determination of the area to be irradiated, toxicity reduction, and optimal escalation of the radiation dose [27, 28]. Interruptions during radiotherapy decrease treatment effectiveness and overall survival of patients receiving cCRT [29]. If the risk of severe radiotherapy complications is high in the opinion of the radiation oncologist, it is more favorable to qualify patients for sequential treatment to reduce the tumor volume during chemotherapy and to conduct radiotherapy in a safe manner.

In all patients qualified for radical treatment, pulmonary function tests (spirometry, gasometry) should be performed, as well as PET-CT and EBUS for evaluation of suspicious lymph nodes. Brain imaging should also be performed before radical treatment in every NSCLC patient. PET-CT examination has crucial importance in radiotherapy planning; meta-analysis results confirmed that in approximately 40% of NSCLC patients target radiotherapy area was significantly changed after PET-CT examination [30]. Another study found that the incorporation of PET into radiation planning can improve local control and reduce toxicity. Therefore, PET-CT imaging should become a standard of care in the radiotherapy planning process [31].

## Consolidation treatment

Consolidation therapy with durvalumab, a monoclonal antibody against the programmed death-ligand 1 (PD-L1), significantly improved treatment outcomes in patients with unresectable stage III NSCLC after successful cCRT. Phase III PACIFIC studies showed that the survival rate in the group receiving durvalumab as consolidation treatment after 12 months from randomization was 83.1% *vs.* 74.6% in the placebo group, after 24 months — 66.3% *vs.* 55.3%, after 36 months — 56.7% *vs.* 43.6%, after 48 months — 49.6% *vs.* 36.3%

and after 60 months — 42.9% *vs.* 33.4%, respectively. In contrast, the percentage of patients achieving 12-month progression-free survival was 55.3% in the group receiving durvalumab as consolidation treatment *vs.* 34.4% in the placebo group, 24month progression free survival (PFS) — 44.8% *vs.* 24.8%, 36month PFS — 39.8 % *vs.* 20.5%, 48-month PFS — 35.3% *vs.* 19.5%, and 60-month PFS — 33.1% *vs.* 19.0%, respectively. The incidence of serious adverse events was similar in both groups [32–35].

Since January 2021, consolidation immunotherapy with durvalumab after cCRT in locally advanced NSCLC has been reimbursed under the B6 drug program [36]. Patients can be enrolled in the program without the need of PD-L1 expression assessment.

## Optimization of treatment in stage III NSCLC patients

The estimates of the National Consultant indicate that in Poland cCRT is used in approximately 300 patients annually, which is at least 3 times less than the real number in need [37]. The reasons for insufficient use of cCRT include delayed lung cancer diagnosis, lack of reference centers, long process of qualification for treatment, and inefficient treatment organization together with service valuation.

In June 2020, a meeting of specialists from the WCO and WCPiT was organized, aimed at determining actions that could improve the management of stage III NSCLC patients. The individual aspects influencing the effectiveness of treatment in Poland are discussed below, and the solutions implemented in the WCO and WCPiT are presented, which have contributed to the improvement of stage III NSCLC treatment (including an increase in the number of patients receiving cCRT).

### Late diagnosis of lung cancer

Lung cancer develops dynamically, and efficient diagnostics allows detection of the disease at the earliest possible stage. In Poland, patients are admitted to pulmonary departments with advanced cancer and often in poor general condition, which makes it impossible to qualify them for cCRT. Primary care physicians may play an important role as their activities may shorten the path from symptom onset to pulmonologist consultation. Activities should, therefore, include shortening the waiting time for a specialist appointment, performing screening tests, and increasing public awareness of lung cancer. Particular attention should be paid to the "at-risk" population (age over 55, current or former smokers). Currently, Poland is implementing the "National Program of Early Lung Cancer Detection Using Low Dose Computed Tomography". It initially covered 6 macroregions, including Poznań, and has recently been extended to the entire country [38]. The program is to last until 2023, and the number of participating institutions is constantly growing.

### Extended process of qualification for treatment

The extended process of qualification for surgery, induction treatment or radiochemotherapy causes patients to be in a more advanced disease stage and worse general condition. Many patients may also require additional imaging tests, which is usually associated with a long turnaround time (TAT) in Polish centers, extension of the diagnostic process, and further delay in treatment initiation. At the WCO and WCPiT, a qualification form for surgery was introduced to assess possible contraindications to surgery during the tumor board and obtain a faster decision of the thoracic surgeon. Moreover, early simultaneous patient qualification for PET-CT and possibly EBUS/EUS, based on CT results, was recommended, which halved the waiting time for examinations and treatment initiation (from two months to a month). At the stage of qualifying for diagnostic tests, the council determines the earliest possible treatment date (adjusted to the dates of diagnostic tests and expected results). Additionally, the patient's general condition and accompanying diseases are analyzed during an interdisciplinary meeting to assess possible contraindications to radiotherapy and chemotherapy.

It should be emphasized that PET-CT examination in patients with stage III NSCLC should be performed routinely, especially in the case of doubts about the patient's eligibility for cCRT or sCRT. However, it is necessary to shorten the duration of diagnostics with imaging tests. According to the Alivia Foundation data, the average waiting time for CT in Poland is 28 days, for MRI — 52 days, and for PET-CT — 21 days [39]. The waiting time varies depending on the voivodship due to the uneven distribution of medical equipment and personnel. Importantly, complete diagnostic tests, along with the correct assessment of the disease stage, allow for quick and accurate treatment decisions during council meetings. At the centers in Poznań, each patient who is tentatively qualified for cCRT is urgently referred for PET-CT examination. Additionally, the date of the planned treatment determined during the council meeting influences the time of the examination.

### Lack of reference centers with multidisciplinary teams

The lack of reference centers with multidisciplinary teams, including pneumonologists, oncologists, thoracic surgeons, radiation oncologist, radiologists,

or pathologists, is another important factor influencing the treatment outcomes in NSCLC patients. Studies have shown that cooperation between specialists in various fields enables the reduction of time from diagnosis to treatment implementation; it also results in increasing the overall survival rate and prolonged progression-free survival time [40]. The NCCN recommends that the lung tumor board discuss both the diagnostic and the treatment process [7]. If the center cannot use both treatment methods (chemotherapy and radiotherapy), it is crucial to strengthen cooperation between teams from different centers. At the WCO, a team of radiation oncologists dedicated to the treatment of lung cancer patients had already been established and now participates in the tumor board and then conducts radiotherapy.

In Poznań centers, NSCLC patients eligible for cCRT have become a priority group (similarly to potentially operable patients) for both specialist doctors and coordinators overseeing the diagnostic and therapeutic path. A pneumonologist refers patients to the tumor board that take place twice a week – it consists of a clinical oncologist, radiologist, radiation oncologist, and thoracic surgeon. During the meeting patients eligible for therapy are discussed, and instructions are given in the case of diagnostic difficulties, indicating the optimal way to establish a diagnosis and further management.

### Treatment toxicity

As already mentioned, cCRT is associated with greater treatment toxicity compared to sCRT or radiotherapy alone, which is of concern for physicians and patients [41]. However, it has been shown that the number of side effects and toxicity grades depend on the type of radiotherapy and chemotherapy regimen [42, 43]. As part of the optimization of cCRT in the WCO and WCPiT, 2 cycles of chemotherapy consisting of cisplatin (75 mg/m$^2$ — day 1) and etoposide (100 mg/m$^2$ — day 1, 2, and 3) are administered in 21-day cycles as it was noticed that the vinorelbine-containing regimen resulted in significant hematological complications after the 8th day of the cycle. In addition, the modern 3D–4D conformal radiotherapy technique is used, which allows limiting the irradiation of healthy tissues due to precise assessment of tumor localization [44]. According to the guidelines, patients receive a total radiation dose of 60 Gy (2 Gy per fraction, 30 fractions). Granulocyte colony-stimulating factors are used prophylactically.

### Organization of treatment

The organization of treatment of NSCLC patients in Poland is also a challenge. The number of centers where both radiotherapy and chemotherapy are available is limited and, therefore, until Lung Cancer Units are established, it is worth developing cooperation between pneumology and oncology departments. It should be noted that cCRT procedure also includes the treatment of possible complications, which is practically impossible in an outpatient setting.

Although the treatment of patients taking place in several centers is associated with certain difficulties (e.g. the need to organize patient transport), the centers in Poznań have proved that the willingness to cooperate allows for good treatment organization, even during the COVID-19 pandemic. For example, considering that group transport often places a heavy burden on cancer patients, weakened by disease and treatment, and increases the risk of infection (especially during the COVID-19 pandemic), it was decided to create special transporting teams. Additionally, patients undergoing cCRT are placed in the same room to limit their contact with other patients. Staff and patients are adequately equipped with personal protective equipment. For patient safety, mandatory tests for the presence of SARS-CoV-2 (performed every 7 days) have been introduced.

## Initial results of optimization

In June 2020, a meeting of a team of specialists from Poznań was held to discuss methods of diagnosis and treatment results in patients with stage III NSCLC. The possibilities for improvement using currently available methods were assessed. Identifying the causes and determining the corrective and optimizing actions, which we have presented in this article, led to a significant increase in the number of patients qualified for cCRT, from 12 patients in both 2018 and 2019 and 2 patients in the first half of 2020 to 30 patients in 2021. Additionally, 12 patients were qualified for consolidation treatment with durvalumab last year. These data confirm the effectiveness of the new strategy and the possibility of a significant improvement in treatment outcomes in patients with stage III NSCLC.

## Conclusions

There is a great need for improvement in the diagnosis and treatment of patients with stage III NSCLC in Poland to ensure they have access to cCRT with possible consolidation treatment. For this purpose, it is necessary to provide adequate training and optimize therapeutic procedures, including 1) education in the field of treatment options for patients with stage III NSCLC, 2) development of dedicated interdisciplinary teams (tumor boards) to establish management and treatment

regimens for patients with early and locally advanced NSCLC, 3) shortening the time of diagnostics by early consultation and qualification to PET-CT examination and, at the same time, for invasive mediastinum evaluation, and 4) prioritization of radical procedures by setting early treatment schedules.

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## Conflict of interest

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