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# Real-World Practice Patterns in the Treatment of Stage III Non-Small Cell Lung Cancer; the Israeli Experience

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## Abstract

**Background:** Stage III Non-Small Cell Lung Cancer (NSCLC) is a highly heterogeneous condition, with many treatment options. We evaluated treatment practices among lung cancer specialists, reasoning that these practices reflect their accumulated real life experience.

**Patients and Methods:** An internet-based survey was conducted among members of the Israeli Society for Clinical Oncology and Radiotherapy involved in the treatment of lung cancer patients. Responses from specialists who have treated at least 100 patients with stage III NSCLC were analyzed.

**Results:** Significant heterogeneity was found. Most participants chose Concomitant Chemoradiotherapy (CCRT) even for poor PS, patients with weight loss and patients with comorbidities. Mediastinal staging prior to CCRT was not deemed required by 46% of the participants. Most responders agreed that following CCRT, surgery may be considered, even for right pneumonectomy, but not if no radiological response is seen.

**Conclusion:** The views expressed by a group of experienced lung cancer specialists differ in some cases from the conclusions of clinical trials. Future prospective studies in stage III NSCLC should attempt to include more defined and homogenous groups of patients, as well as patients with co-morbid conditions in order to arrive at widely accepted conclusions.

**Keywords: Chemoradiotherapy; Internet-based survey; Neoadjuvant; Tri-modality; Single-station N2**

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## Introduction

Lung cancer is the most common cause for cancer-related death world-wide as well as in Israel [1,2]. It is characterized by diagnosis at a late stage and by a poor response to treatments. Approximately one third of Non-Small Cell Lung Cancer (NSCLC) patients present with stage III, locally advanced disease. Stage III NSCLC encompasses a wide range of clinical presentations including large primary T4 tumors with no lymph node involvement on one hand and bulky mediastinal or supraclavicular nodal disease on the other hand. Based on similar overall survival outcomes, stage III NSCLC was grouped together under two headings of stage IIIA and IIIB, to facilitate comparisons in clinical trials and retrospective analyses. However, the heterogeneity in disease burden and distribution of spread may actually suggest that different treatment protocols should be utilized in distinct stage III NSCLC patients. The large variability of disease pattern might explain the inconsistent reports about the efficacy of specific treatment regimens for these patients.

Historically, unresectable stage III NSCLC has been treated by radiotherapy alone, until two randomized trials demonstrated that addition of chemotherapy improves outcome [3-5]. Currently, Concurrent Chemoradiation (CCRT) is the most widely accepted standard of care for stage IIIA/IIIB NSCLC [6,7]. This is based on a number of randomized trials and a meta-analysis demonstrating a 5-year absolute survival improvement of 4.5% with CCRT in comparison to

**Table 1:** Questionnaire submitted to survey participants.
Free text answers were optional where required.

| | Question | Optional answers | |
|---|---|---|---|
| 1 | How many stage III NSCLC patients did you treat (treat means patients that signed informed consent with you and wrote the treatment plan) ever (throughout your career)? | 1-20 | |
| | | 20-40 | |
| | | 40-100 | |
| | | More than 100 | |
| 2 | Your specialty; Are you a certified: | Medical Oncologist | |
| | | Radiation Oncologist | |
| | | Both Medical and Radiation Oncologist | |
| | | Other, please specify | |
| 3 | Case scenarios, NSCLC stage III, no surgical option | | |
| | (a) Good PS, no wt loss, no significant comorbidities | All options for each scenario | Concomitant chemoradiation |
| | (b) PS 2 | | Sequential chemoradiation |
| | (c) Good PS (0-1) but weight loss >10% in 3 months | | Only systemic therapy |
| | (d) Good PS, no wt loss, but diabetes on oral drugs | | Only radiotherapy |
| | (e) Good PS, no wt loss, but CRF, creatinine >2 | | Best supportive care |
| 4 | Is there an age above which you would not give concomitant chemoradiation for stage III NSCLC? | No, age is not a factor by itself | |
| | | Yes, 75 is the limit | |
| | | Yes, 80 is the limit | |
| | | Yes, 85 is the limit | |
| | | Other, please specify... | |
| 5 | The chemotherapy given as part of definitive chemoradiation: | Cisplatin Vinorelbine | |
| | | Cisplatin Etoposide (SWOG protocol) | |
| | | Cisplatin Pemetrexed | |
| | | Carboplatin Pemetrexed | |
| | | Carboplatin Paclitaxel | |
| | | Other | |
| 6 | Specific regimen you mostly use - doses, schedule; Dose in mg/m2, frequency: | | |
| 7 | Dose of radiotherapy you recommend for fit patients undergoing concomitant definitive chemoradiation; cGy total - number of fractions: | | |
| 8 | Surgery after concomitant chemoradiation | Is not a reasonable option | |
| | | Can be considered in selected cases (i.e good response to chemoradiation, limited mediastinal involvement, good PS, lobectomy planned) | |
| | | Should always be considered if a surgeon is willing to operate | |
| 9 | The following conditions: | | |
| | (a) Would you consider surgery after concomitant chemoradiation? | All options for each scenario | Surgery is never an option |
| | (b) 60 Gy given | | |
| | (c) Left pneumonectomy would be required | | Surgery can be considered in selected cases |
| | (d) Right pneumonectomy would be required | | |
| | (e) Stable disease following chemoradiation | | Surgery should always be considered |
| | (f) Good response after chemoradiation radiologically, but mediastinoscopy positive after chemoradiation | | |
| | (g) Good response radiologically after chemoradiation, mediastinoscopy negative after chemoradiation | | |
| | (h) Good response radiologically after chemoradiation, mediastinoscopy not done after chemoradiation | | |
| 10 | The following conditions: would you suggest neo-adjuvant treatment, planning for surgery afterwards? | | |
| | (a) Stage III N2 disease, 2-3 nodal stations | No need for neo-adjuvant therapy, direct surgery / Consider neo-adjuvant chemotherapy / Consider neo-adjuvant chemo-rads / Surgery is not an option | |
| | (b) Stage III, single station N2 node | | |
| | (c) Stage III, no N2 nodes at all | | |

| | | |
|---|---|---|
| 11 | Neo-adjuvant treatment for stage III | Mediastinum should be sampled before and after treatment, before surgery |
| | | Mediastinum should be sampled after treatment, before surgery |
| | | Mediastinum should be sampled only on initial staging |
| | | No need to sample the mediastinum, CT-PET is good enough |
| | | Neo-adjuvant treatment is not an option for stage III |
| 12 | Continuing chemotherapy after definitive chemoradiation | No need, stop chemotherapy at end of radiation |
| | | If fit, continue to complete 4 cycles total |
| | | If fit and any disease left by CT, continue as for metastatic disease |
| | | If fit and any disease left by CT-PET, continue as for metastatic disease |
| 13 | Follow up after definitive chemoradiation | CT-PET only |
| | | CT (not PET) only |
| | | CT and CT-PET |
| 14 | Your name and institution | |

PS: Performance Status. Wt: Weight. SWOG: South West Oncology Group. PET: Positron Emission Tomography.

**Table 2:** Experienced specialists' responses regarding treatment choice for stage III NSCLC
Percentages of the provided answers are shown for each case (question 3 in Table 1).

| Item in Table 1, question 3 | Clinical Scenario | CCRT | Sequential | RT only | Chemo only |
|---|---|---|---|---|---|
| a | Stage III | 100.0 | 0.0 | 0.0 | 0.0 |
| b | PS = 2 | 46.2 | 30.8 | 7.7 | 15.4 |
| c | Weight loss >10% in 3 months | 83.3 | 16.7 | 0.0 | 0.0 |
| d | Diabetes Mellitus on oral drugs | 100 | 0.0 | 0.0 | 0.0 |
| e | CRF, creatinine >2 gr / dL | 53.8 | 23.1 | 23.1 | 0.0 |

CCRT: Concomitant Chemoradiation; Sequential: Sequential Chemoradiation; RT: Radiotherapy; Chemo: Chemotherapy; PS: Performance Status; Wt loss: more than 10% weight loss in 3 months; CRF: Chronic Renal Failure; See detailed questions in Table 1 under question 3.

sequential treatment (hazard ratio, HR =0.84) [8]. Only esophageal toxicity was significantly elevated in the concomitant treatment group. However, patients included in these trials usually had other good prognostic features including a good Performance Status (PS), minimal weight loss and no significant comorbidities. In practice, the common NSCLC patient is elderly, frail and with potentially significant comorbidities, thereby not resembling the patients in clinical trials. Unlike the data regarding patient assessment prior to surgery, no clear evidence or guidelines exist regarding required lung function or other parameters for candidates for CCRT.

One of the major unresolved issues regarding stage III NSCLC is the role of surgery. Only a small number of Randomized Clinical Trials (RCT) has attempted to answer this question. The most relevant study that included modern CCRT was the intergroup 0139 study, which randomized potentially resectable stage IIIA-N2 patients to definitive chemoradiation to 61 Gy with concomitant chemotherapy (cisplatin and etoposide) versus chemoradiation to 45 Gy followed by surgery [9]. No survival benefit was demonstrated despite an improvement in Progression Free Survival (PFS; HR 0.77). An unplanned subgroup analysis of the study demonstrated improved OS with tri-modality treatment when lobectomy and not pneumonectomy was performed. Possible explanations for these results include the unacceptably high perioperative mortality rate following pneumonectomy and the relatively low dose of radiotherapy in the surgical group. The best outcome was achieved in patients that had mediastinal down-staging with CCRT. These results suggest that tri-modality treatment for stage IIIA-N2 NSCLC may be an option in cases demonstrating a good response to neoadjuvant chemoradiation, mainly when lobectomy is feasible. Another study that compared CCRT followed by surgery or by additional CCRT reported no differences in OS or in PFS [10]. In light of these results, current practice varies significantly among institutions and countries.

Another unresolved issue in the treatment of stage III patients relates to the recommended dose of radiotherapy. Dose escalation has been attempted and single arm studies have reported improved outcomes [11]. However, this has been questioned in light of the recent RTOG 0617 trial that reported a detrimental impact of dose escalation from 60 Gy to 74 Gy in stage IIIA/IIIB patients [12,13]. Higher risk of death on the high-dose was not driven by access treatment-related deaths, making this result difficult to explain, possibly related to late cardiac toxicity.

The direct result of the heterogeneity of stage III disease and reported clinical trials is the apparent laxity of recommended treatment guidelines [6,7]. Uncertainty exists about most of the clinical issues regarding stage III NSCLC. These include the role of tri-modality treatment, the choice of chemotherapy drugs and doses, the choice of radiotherapy dose, number of chemotherapy cycles and questions regarding mediastinal sampling. Definition of more homogenous sub-groups of the very heterogeneous group of stage III NSCLC might allow better risk stratification and better designed studies. The goal of this study was to evaluate the views regarding these questions among the Israel Lung Cancer Group members. Since personal opinions of experienced physicians are based upon their accumulated real-life experience, clinical practice patterns may provide information that sometimes cannot be gained from clinical trials.

## Materials and Methods

During February 2013, an internet-based survey was sent by email to all physician members of the Israel Lung Cancer Group

**Table 3:** Experienced specialists' responses regarding surgery after chemoradiation
Percentages of the provided answers are shown for each case (question 9 in Table 1).

| Item in Table 1, question 9 | Clinical Scenario | Always | Can be considered | Never |
|---|---|---|---|---|
| a | Surgery after chemoradiation | 7.7 | 92.3 | 0.0 |
| b | Following 60 Gy RT dose | 0.0 | 91.7 | 8.3 |
| c | Left pneumonectomy required | 0.0 | 75.0 | 25.0 |
| d | Right pneumonectomy required | 0.0 | 63.6 | 36.4 |
| e | Stable disease following CCRT | 0.0 | 27.3 | 72.7 |
| f | Good radiologic response, mediastinum positive | 0.0 | 50.0 | 50.0 |
| g | Good radiologic response, mediastinum negative | 25.0 | 66.7 | 8.3 |
| h | Good radiologic response, mediastinum not sampled | 0.0 | 100.0 | 0.0 |

Always: Surgery should always be considered; Can be considered: surgery can be considered in selected cases; Never: Surgery should never be considered; RT: Radiotherapy; Mediastinum positive/negative: refers to pathologic staging results.

**Table 4:** Experienced specialists' responses regarding neoadjuvant treatment approach for patients with stage III NSCLC
Percentages of the provided answers are shown for each case (question 10, Table 1).

| Item in Table 1, question 10 | Clinical Scenario | Upfront surgery | Neoadj Chemorad | Neoadj Chemo | No role for Surgery |
|---|---|---|---|---|---|
| a | 2-3 N2 station LNs involved | 0.0 | 38.5 | 23.1 | 38.5 |
| b | Single N2 station LN involved | 7.7 | 69.2 | 23.1 | 0.0 |
| c | No N2 nodes involved | 30.8 | 30.8 | 23.1 | 15.4 |

Neoadj: Neoadjuvant; Chemorad: Chemoradiation; Chemo: Chemotherapy; LN: Lymph Nodes.

(ILCG), including 39 Medical Oncologists, Radiation Oncologists and Pulmonologists. Results were collected using fluid survey (http://fluidsurveys.com) website. The survey included 13 multiple-choice questions and one question regarding participants contact information (Table 1). Only the responses of specialists with experience in treating stage III NSCLC, defined as treating at least 100 such patients throughout their career, were analyzed (N =15).

The trial protocol has been approved by the Sheba Medical Center ethical committee and thus meets the standards of the Declaration of Helsinki in its revised version of 1975 and its amendments of 1983, 1989, and 1996. Local institutional review board of the Sheba Medical Center approved the protocol (approval 0257-13-SMC), the requirement for written informed consent was waived.

## Results

**Survey participants:** Out of 39 the physicians approached, 19 completed the online survey (48.7%). To ensure reliability of the data and to avoid accidental duplicate answers, only data entered by an identified lung cancer specialist were considered; therefore one submitted survey was excluded due to missing identifiers of the responding physician.

Ten of the 18 identified participants are certified Medical Oncologists, 7 are certified as both Medical and Radiation Oncologists, and one is a Radiation Oncologist. One of Medical Oncologists is also a certified Pulmonologist. Fifteen of the responders (83%) reported treating more than 100 stage III NSCLC patients throughout their career and their responses were analyzed as described below and reported in this manuscript. These 15 participants practice in a total of 12 different Oncology Departments or Institutes, including the 7 largest hospitals of Israel.

**Definitive chemoradiation treatment:** The first set of questions was related to the approach to a stage III NSCLC with no surgical option and was presented as case scenarios, each with five optional answers (Table 1). The questions related to stage IIIA and IIIB disease as single entity. The percentages of specialists that chose each option are presented in Table 2.

Participants were asked about an age above which they would not consider CCRT as an option (question 4). 76.9% did not consider age as a factor on its own, 15.4% considered age of 80 years as the maximal for CCRT and 7.7% thought 75 years is the maximum.

The commonly used chemotherapy regimens chosen for definitive chemoradiation (Table 1, questions 5-6) are presented in Figure 1. One of the suggested regimens was histology-based (cisplatin-pemetrexed for adenocarcinoma and cisplatin- vinorelbine/cisplatin-docetaxel for non-adenocarcinoma). Variability was present within each chemotherapy indicated, with cisplatin and vinorelbine given either as weekly treatments (cisplatin 20 mg/m2, vinorelbine 15 mg/m$^2$ to 25 mg/m$^2$) or in 2 out of every 3 weeks regimen (cisplatin 70 mg/m$^2$ q 21 days with vinorelbine 15 mg/m$^2$ D1, D8 q 21 days; or cisplatin 37.5 mg/m$^2$ with vinorelbine 12.5 mg/m$^2$ D1, D8 q 21 days); Carboplatin and paclitaxel regimens were of weekly (carboplatin 2 AUC and paclitaxel 40 mg/m$^2$, q wk) or q 21 days regimens (carboplatin 6 AUC and paclitaxel 200 mg/m$^2$ q to 225 mg/m$^2$ q 21 days). The cisplatin and etoposide regimen was the South West Oncology Group (SWOG) protocol (cisplatin 50 mg/m$^2$ D1, D8, etoposide 50 mg/m$^2$ D1-D5, given at 1$^{st}$ and 5$^{th}$ week of radiotherapy) [9].

When asked about the recommended radiotherapy dose for definitive CRT, 61.5% of participants chose a dose of 60 Gy or less (range 50.4 Gy to 60 Gy), while 38.5% choose more than 60 Gy (range 64 Gy to 72 Gy; question 7 in Table 1).

The approach to consolidation treatment after completion of definitive chemoradiation was evaluated (Table 1, question 12). 46.2% opted to continue chemotherapy aiming for completion of four cycles of chemotherapy treatment, while the same proportion (46.2%) chose to stop chemotherapy when radiotherapy is complete. One specialist (7.7%) indicated that if any remaining disease is present, treatment should continue as for stage 4 disease.

Participants were asked about their choice of follow up modality after completion of definitive chemoradiation (question 13). The

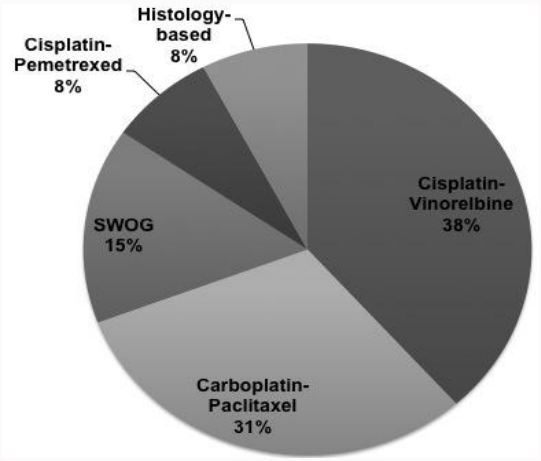


**Figure 1:** Participants' choice of chemotherapy regimen to be used as part of definitive concomitant chemoradiation.

majority of specialists (53.8%) chose to use both Computerized Tomography (CT) studies as well as combined CT-Positron Emission Tomography (CT-PET) studies. CT-PET only was the choice in 30.4% and CT only was the choice in 15.4%.

**The role of surgery:** The following set of questions was focused on the approach to surgery following chemoradiation (questions 8-9 in Table 1). As for the previous questions, stage III designation was mentioned with no referral to stage IIIA vs. IIIB. The percentages of specialists choosing each option are shown in Table 3.

A set of questions examined the approach towards neoadjuvant therapy for various subtypes of stage IIIA disease (question 10 in Table 1). Several case scenarios were presented with multiple-choice answers.

The timing chosen for mediastinal sampling was queried (question 11). 38.5% of the participants considered mediastinal sampling to be required only before neoadjuvant treatment, 23.1% thought it is required only after the treatment and prior to surgery, while 15.4% indicated the need to mediastinal staging both before and after neoadjuvant treatment. 23.1% suggested CT-PET is sufficient for reliable mediastinal staging.

## Discussion

Stage III NSCLC is a heterogeneous condition, comprised of several distinct patterns of spread. Despite improvements in diagnosis, staging and treatments over the last 20–30 years, the majority of stage III NSCLC patients will succumb to the disease. Distant relapse is the main cause of disease failure [4,8,9]. Both aggressive local-regional treatment as well as better systemic treatment may increase the cure rate. Currently there is no way of predicting distant spread, and therefore the role of maximizing systemic therapy versus concentrating on local-regional treatment is uncertain. In this study we have attempted to gain insight into the treatment strategies of experienced lung cancer specialists regarding stage III NSCLC.

Heterogeneity of the disease encourages treatment tactics variability, as found in this study. In fact, unanimous responses were seen only regarding the choice of CCRT for a fit non-resectable stage III NSCLC with no weight loss and good renal function. All cases with some clinical challenge that might impede on CCRT safety or efficacy elicited a large range of responses, from an aggressive approach of CCRT to a gentle single modality approach (Table 2). Comorbidities are well-recognized poor prognostic factors although to the best of our knowledge, a detailed examination of specific comorbid factors related to treatment outcomes has not been performed [14]. Interestingly, diabetes mellitus was unanimously regarded as not precluding CCRT, while almost half of the respondents thought elevated creatinine (>2 mg/dL) does not allow for CCRT; possibly reflecting personal experience. Choices of chemotherapy agents, doses, schedule and choices of radiotherapy doses were also within a wide range, compatible with published treatment regimens [7].

Regarding a surgical option following CCRT, there was a general consensus that it has a role in selected cases, but the majority considered it irrelevant if no radiological response was seen following CCRT (Table 3). The questions presented no specification regarding stage IIIA vs. IIIB, reflecting the lack of this distinction in many of the studies [6,8]. Half of the respondents would consider a surgical approach after a good radiological response, even if the mediastinum did not achieve a complete response. This point of view is compatible with the fact that only a third of respondents considered mediastinal sampling to be required after neo-adjuvant treatment. Interestingly, most participants considered pneumonectomy an option after CCRT, in spite of the poor results reported in the intergroup 0139 study [9]. Personal experience of some of the participants as well as small series reporting favorable outcome support the notion that peri-operative mortality in experienced centers is not as high as reported in the intergroup 0139 study [15-17]. The surgical solutions to the problem of poor wound healing after high-dose radiotherapy are well recognized [18].

Neoadjuvant treatment approach for a patient with a single N2 station involvement was accepted by most specialists. The choice of neoadjuvant treatment varied between chemoradiation and chemotherapy alone. Indeed, neoadjuvant chemotherapy confers a survival benefit [19-21], apparently similar to that of adjuvant chemotherapy [22,23]. Addition of radiotherapy or chemoradiation to the neoadjuvant regimen increases response rate and pathological down-staging with inconsistent impact on patient outcome [24,25].

The conflicting results in trials for stage III NSCLC result in inconsistent patterns of practice. In our study, a favorable opinion was seen towards surgery for stage III patients (Tables 3 and 4). Additional studies might reveal if the cause for this position is based on favorable results in real life experience, small reported case series or a bias towards a surgical solution. Sub-classification of stage III based on mediastinal burden of disease has been suggested in the past [26]. Such refinement in the definition of exent of disease is to be encoraged. Future prospective studies in stage III NSCLC should attempt to include more defined and homogenous groups of patients in order to arrive at widely accepted conclusions.

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