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Feasibility of Concomitant Chemoradiotherapy in Daily Practice for Patients with NSCLC Stage III

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Abstract. *Background: In patients with non-small cell lung cancer (NSCLC), approximately 25% have locally advanced disease. For patients with irresectable (N2-3 or T4) or inoperable disease, treatment consists of chemoradiotherapy. Concomitant chemoradiotherapy improves survival compared to sequential chemoradiotherapy in these patients. Patients and Methods: Treatment plans and completion of treatment was evaluated for all patients treated at the St. Antonius Hospital from 2008-2011 for NSCLC stage IIIA/B not eligible for surgery. Results: Between 2008 and 2011, 180 patients with NSCLC stage III were treated at our hospital. A total of 152 patients were not eligible for surgery; in 78 (51%) patients, primary treatment was chemoradiotherapy; 31 (20%) were planned for concomitant treatment. The most frequent reasons for refraining from concomitant chemoradiotherapy were limitations of radiotherapy constraints and condition of the patients (87%). Conclusion: Although concomitant chemoradiotherapy is the standard-of-care in patients with stage IIIA/B NSCLC ineligible for surgery, the majority (80%) of the patients were treated otherwise.*

For patients with non-small cell lung cancer (NSCLC) stage IIIA/B who are ineligible for surgery [irresectable (N2-3 or T4) or inoperable], the standard treatment consists of concomitant chemoradiotherapy (1). Combining chemotherapy with thoracic radiotherapy demonstrated a survival benefit when compared to thoracic radiotherapy alone [absolute benefit of 2% at 2 years; relative risk of death at 2 years 0.87, 95% confidence interval (CI)=0.81-0.94; pooled odds ratio at 2 years 0.70, 95% CI=0.5-0.9) (2-4).

Concomitant chemoradiotherapy improves survival compared to sequential treatment in patients with locally advanced NSCLC (increase in median survival of 1-3.4 months) (5, 6). However this treatment has shown higher toxicity than sequential chemoradiotherapy. A meta-analysis demonstrated a higher risk of acute grade 3-4 esophageal toxicity in concomitant *versus* sequential chemoradiotherapy (18% *vs.* 4%) (6). No difference was seen in subgroups based on age, sex, histology, tumor stage or performance score. Although concomitant chemoradiotherapy is the standard treatment, it has a higher toxicity and might not be feasible for all patients.

Indications to refrain from chemoradiotherapy and opt for palliative treatment with chemotherapy, radiotherapy, local therapy or best supportive care are: Eastern Cooperative Oncology Group performance score (ECOG PS) greater than 2, advanced age (>80 years), co-morbidities [American Society of Anesthesiologists classification (ASA) class >3], contra-indications for chemotherapy or radiotherapy (*e.g.* renal insufficiency or pulmonary fibrosis), limitations of radiation due to organs at risk (exceeding the radiotherapy constraints, see Table I), other acute treatment indications (such as radiotherapy for hemoptysis or a superior vena cava syndrome) and patient desire.

If a patient can be treated with chemoradiotherapy, the patient is eligible for concomitant treatment when the patient has an ECOG PS 0-1 and limited comorbidity (ASA class 1 and 2).

We intended to examine treatment plans and completion of treatment at our hospital in patients with NSCLC stage III who were not eligible for surgery. We hypothesized based on previously mentioned studies that most patients would be treated with concomitant chemoradiotherapy and complete this treatment.

Patients and Methods

We performed a retrospective cohort study. A hospital database of all lung cancer patients treated at the St. Antonius Hospital Nieuwegein was explored to review treatment plans and completion

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Key Words: Non-small cell lung carcinoma, stage III, chemo-radiotherapy, therapy.

Table I. *Tissue dose–volume constraints for conventional fractionated radiotherapy.*

Organ	Constraints	
Myelum	D_{max} 50 Gy (EQD2, α/β=2 Gy)	
Lungs	Lung GTV, V20Gy <35%, mean lung dose <20 Gy	
Esophagus	Mean dose ≤45 Gy	No solid constraint, for registration
Hart	Mean dose ≤45Gy	No solid constraint, for registration
Plexus	66 Gy	No solid constraint, for registration

D_{max}: Maximum dose; EQD2: equivalent dose in 2Gy fraction; GTV: gross tumor volume; V20Gy: volume receiving 20Gy or more.

Table II. *Primary treatment plan.*

Treatment	Disease stage IIIA	Disease stage IIIB	Total N (%)
Chemoradiation, n	39	39	78 (51)
Concomitant	21	10	31 (20)
Sequential	18	29	47 (31)
Chemotherapy, n	7	15	22 (14)
Radiotherapy, n	10	6	16 (11)
Best supportive care, n	16	16	32 (21)
Other, n	3	1	4 (3)
Total	75	77	152

switched to sequential treatment at their request, another patient's condition deteriorated and the last patient had a suspicion of a cerebral metastasis or primary tumor. In two patients, treatment was interrupted by toxicity, both developed a pulmonary infection. In one patient, no reason to discontinue treatment was documented.

In 15 out of the 47 patients planned for sequential therapy, treatment was not completed. One patient died before

Table III. *Characteristics of patients planned for chemoradiotherapy.*

	Chemoradiotherapy type		
	Concomitant	Sequential	*p*-Value
Number of patients	31	47	
Mean age, years	60	64	0.167
ECOG performance score, n			0.370
0-1	23	33	
>1	2	7	
>2	0	2	
Unknown	6	7	
Co-morbidity/ASA score			0.128
1	15	14	
2	12	16	
3	3	14	
Unknown	1	3	
Mean FEV1, l	0.76	0.71	0.354
Unknown (n)	8	13	
Stage			0.005
IIIA	23	20	
IIIB	8	27	
Mean survival from diagnosis, days	934	595	0.058

FEV1: Forced expiratory volume; ECOG: Eastern Cooperative Oncology Group; ASA: American Society of Anesthesiologists classification.

or IIIB disease was significantly different between the groups treated concomitantly or sequentially.

In a meta-analysis of toxicity, mainly esophageal toxicity was higher in those undergoing concomitant treatment compared to those undergoing sequential treatment (6). In our cohort, toxicity or discontinuation of treatment in the concomitantly treated group was not significantly different: in 2 out of the 31 (6%) concomitantly treated patients and 4 out of the 47 (8%) sequentially treated patients, toxicity caused discontinuation of therapy. The total discontinuation rate was 11 out of 31 (35%) in concomitantly treated patients and 15 out of the 47 (32%) sequentially treated patients. The current criteria seem appropriate to select patients for concomitant treatment.

Limitations of this study are the small sample size and the retrospective design. For some patients, the reason for the choice of therapy was not found in the electronic patient record. The feasibility to treat with (concomitant) chemoradiotherapy was assessed in a multidisciplinary tumor board. Some patients exceeded the radiotherapy constraints at the intake/planning CT at the Radiotherapy Department. This was scored as discontinuation of treatment and may have negatively influenced our estimation of treatment feasibility.

Conclusion

Although concurrent chemoradiotherapy is the standard treatment for patients with stage III A/B NSCLC who are not eligible for surgery, only 20% of patients were treated with concomitant chemoradiotherapy. Reasons for refraining from concomitant treatment were exceeding radiotherapy constraints and poor condition of the patient. This might be related to the significantly higher number of patients with stage IIIB disease in the sequential treatment group. In patients planned for concurrent treatment, no greater toxicity or discontinuation of treatment was seen compared to patients planned for sequential treatment.

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