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Treatment patterns and clinical outcomes in stage III non-small-cell lung cancer: a long-term institutional experience in Switzerland

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Summary

STUDY AIM: Treatment of stage III non-small-cell lung cancer (NSCLC) has evolved rapidly in recent years. To improve our understanding of real-world outcomes in Switzerland, we report on our institutional experience at an academic lung cancer centre and describe treatment patterns and clinical outcomes over a multi-year period.

METHODS: Patients diagnosed with stage III NSCLC between 2013 and 2023 were included in an ethics-approved institutional database. Based on tumour board decisions, the initial treatment strategy was defined for each patient. Overall and progression-free survival were calculated using the Kaplan-Meier method. A multivariate Cox regression analysis was performed to study the impact of different factors on clinical outcomes.

RESULTS: A total of 315 patients with stage III NSCLC were included. Patients were a median of 68 years old, and two-thirds were male. The most common stage at diagnosis was IIIA (56%), followed by stage IIIB (36%) and IIIC (8%). A curative treatment approach was pursued in 88% of patients, and over 90% of these received definitive local treatment (surgery and/or radiotherapy). Rates of 1-year overall and progression-free survival improved from 64% and 47%, respectively, in 2013–2016, to 82% and 70% in 2020–2023. However, 49% of patients developed locoregional and/or distant recurrence. Results of the multivariate analysis are presented in the manuscript.

CONCLUSIONS: Almost 90% of patients with stage III NSCLC underwent treatment with curative intent, with rates of treatment adherence that compared favourably to the literature. Although survival outcomes appear to have improved in recent years, the rates of disease recurrence remain high, reflecting a need for further improvements.

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Introduction

Lung cancer is the most commonly diagnosed cancer worldwide, accounting for around 2.5 million new cases (or 12.4% of all cancers) in 2022. Lung cancer is also the leading cause of cancer mortality, responsible for around 1.8 million deaths (or 18.7% of all cancer deaths) annually [1]. Population-level analyses suggest that lung cancer mortality has decreased in some countries, which may be attributed to substantial advances in lung cancer treatment in recent years [2]. However, the global burden of disease remains high, and clinicians and patients alike are faced with a treatment landscape of increasing complexity.

Non-small-cell lung cancer (NSCLC) accounts for approximately 85% of all lung cancers [3]. Around 30% of patients with NSCLC are diagnosed with stage III disease, which comprises a heterogeneous group of patients, including tumours with advanced local infiltration, or mediastinal lymph node metastases, among other criteria [4, 5]. The treatment of stage III NSCLC has evolved rapidly in recent years. In particular, the introduction of immune checkpoint inhibitors (ICI) has changed the standard of care for both resectable and unresectable patients [6–9]. Despite these advances, the management of patients with locally advanced NSCLC remains challenging, as most patients will eventually develop a recurrence. In addition, patients are often elderly and comorbid, and large variations exist in real-world treatment patterns [5, 10, 11]. Treatment decision-making may thus differ between institutions based on local expertise, as well as expert opinion, in this rapidly evolving field.

We analysed treatment patterns and clinical outcomes in patients with stage III NSCLC who underwent treatment at our institution over a multi-year period. Considering the evolution of treatment approaches over this time, we aimed to understand how this has influenced the treatment of stage III NSCLC in a real-world setting. Furthermore, we studied survival and recurrence patterns to improve our

understanding of treatment outcomes in the contemporary setting.

Materials and methods

We conducted a retrospective analysis of patients who underwent treatment for stage III NSCLC at the University Hospital of Basel in Basel, Switzerland. The University Hospital of Basel is a tertiary academic centre, and the largest provider of thoracic oncology services in Northwestern Switzerland. The project was approved by the Ethics Committee of Northwestern and Central Switzerland (BASEC ID 2023-01712). No external funding was received for the planning or conduct of this study.

All patients newly diagnosed with stage III NSCLC between 1 January 2013 and 31 December 2023 were considered eligible for the analysis. Patients with a documented refusal of consent for data analysis for research purposes were excluded. Patients were identified through a multi-stage process, based on the thoracic tumour board reports. Electronic tumour board reports were searched for terms associated with stage III NSCLC (including "stage III", "locally advanced" and "locoregionally advanced"). The resulting list as well as all individual tumour board reports (including non-searchable documents generated before 2017) were manually cross-checked for validity and completion.

All patient data was anonymised using an external data catalogue and stored on a study-specific Castor EDC platform (Castor, USA). Patient and tumour characteristics, as well as follow-up data, were manually collected from electronic medical records. Patients were generally staged using 18F-fluorodeoxyglucose (FDG) positron emission tomography (PET) and magnetic resonance imaging (MRI) of the brain. Mediastinal staging was performed using bronchoscopy ± endobronchial ultrasound (EBUS) and/or mediastinoscopy in accordance with clinical practice guidelines [12]. NSCLC stage was defined based on the 8th edition of TNM staging for lung cancer [13]. Cases that had been staged using the 7th edition (prior to 2017) were manually verified and redefined according to the 8th edition, if necessary. Pathological stage was considered in patients undergoing primary surgery, but not after any neoadjuvant treatment due to possible downstaging. Based on tumour board recommendations and/or individual consultations, the treatment strategy was documented for each patient: primary surgery with adjuvant therapy, neoadjuvant treatment before surgery, definitive chemoradiotherapy, palliative therapy (radiotherapy, systemic therapy or both) or best supportive care.

Overall survival was calculated from the time of diagnosis (based on histology/cytology) to death using the Kaplan-Meier method. Progression-free survival was defined as the time from diagnosis until disease progression or death. Sites of first recurrence were manually confirmed and categorised as follows: locoregional (ipsilateral lung and/or regional lymph node), distant lung, brain metastases, other extracranial metastases or new primary lung tumours. A multivariate Cox regression analysis was performed to calculate the hazard ratio (HR) of progression-free survival in patients who were treated with curative intent and followed for at least two years. Statistical analyses were performed using RStudio version 2024.04.1+748 (RStudio, USA).

Results

Patient characteristics

A total of 315 patients were included in the analysis. Baseline patient characteristics are summarised in table 1. Patients were a median of 68 years old (range: 35–92) at time of diagnosis. The proportion of male and female patients was 66% and 34%, respectively, and most patients (92%) had a smoking history. Patients were most commonly diagnosed with adenocarcinoma (50%), followed by squamous cell carcinoma (43%), NSCLC-Not Otherwise Specified (4%) and large cell neuroendocrine carcinoma (LCNEC; 3%). The most common stage at diagnosis was IIIA (56%), followed by stage IIIB (36%) and IIIC (8%). Predictive biomarker testing was performed in 82% of patients with non-squamous histology (n = 180) and 19% of patients with squamous histology (n = 135). Among patients with non-squamous histology who underwent testing (n = 148), targetable driver mutations in the epidermal growth factor receptor *(EGFR)* or anaplastic lymphoma kinase *(ALK)* genes were found in 8 (5%) and 4 (3%) patients, respectively. Other tested patients had either no actionable driver alterations, or other mutations that were not actionable at that time. This included all patients with squamous histology, although these were only selectively tested (e.g. young age, non-smokers).

Treatment patterns

Baseline treatment characteristics are summarised in table 1. Primary surgery followed by adjuvant therapy (37% of all patients) and neoadjuvant treatment before surgery (35%) were the most frequent treatment approaches used, followed by definitive chemoradiotherapy (17%) and palliative treatments (12%; see table 1 for details). Twenty-three patients (7%) were treated within clinical trials. The distribution of treatment strategies over time is visualised in appendix figure S1.

A summary of patients who underwent treatment with curative intent (n = 277) is shown in figure 1, with details on systemic therapies provided in appendix figure S2. The median time from diagnosis to treatment was 26 days. In the primary surgery group (n = 115), 96 patients (83%) had stage IIIA disease and 114 (99%) did undergo definitive surgery, with one patient dying prior to the planned procedure. Seventy-one patients (62%) subsequently received adjuvant chemotherapy, most commonly with cisplatin / vinorelbine, and 20 patients (18%) underwent postoperative radiotherapy (PORT). In 42 patients who did not receive adjuvant chemotherapy, reasons were patient preference (n = 17), poor general condition (n = 17), death (n = 5), delay >6 months due to protracted course with repeated surgeries (n = 1), atypical carcinoid histology (n = 1) and preference for adjuvant tyrosine kinase inhibitor (TKI) alone (n = 1; patient with epidermal growth factor receptor mutation).

In the neoadjuvant group (n = 109), 57 patients (52%) had stage IIIA disease. The most common regimen for induction chemotherapy was cisplatin/docetaxel, and additional neoadjuvant immune checkpoint inhibitors and/or radiotherapy were administered in 23% and 26% of patients,

respectively. Following induction, 100 patients (92%) underwent definitive surgery, with 9 patients not undergoing surgery due to unresectable disease (n = 3), medical inoperability (n = 3), progressive disease (n = 1), patient refusal (n = 1) and death (n = 1). One additional patient was found to be unresectable during surgery. Following resection, 17% of patients received adjuvant immune checkpoint inhibitors and/or postoperative radiotherapy (details see figure 2 and appendix figure S2).

In the chemoradiotherapy group (n = 53), 15 patients (28%) had stage IIIA disease. Concurrent and sequential chemoradiotherapy was administered in 89% and 11% of patients, respectively. Patients received a median of 4 cycles (range: 1–7) of chemotherapy, and radiotherapy was delivered with a median of 60 Gy (range: 0–69). Cisplatin-based chemotherapy regimens were administered in 19% of patients. The most frequently used chemotherapy regimen was carboplatin/paclitaxel (51%), followed by carboplatin/pemetrexed (21%) and cisplatin/etoposide (15%). Five patients (9%) did not receive radiotherapy, and two additional patients received less than 50 Gy. Following chemoradiotherapy, 27 patients (56%) received consolidation immune checkpoint inhibitors. This rate was 76% after approval of durvalumab in 2018.

Clinical outcomes

The Kaplan-Meier estimates of overall and progression-free survival for the full cohort are visualised in appendix

Table 1:
Characteristics of patients diagnosed with stage III non-small-cell lung cancer (NSCLC) between 2013 and 2023.

			Patients (n = 315)
Age in years, median (range)			68 (35–92)
Sex, n (%)	Male		209 (66)
	Female		106 (34)
Smoking history, n (%)	Never		23 (7)
	Former		111 (35)
	Current		181 (57)
Histology, n (%)	Adenocarcinoma		157 (50)
	Squamous cell carcinoma		135 (43)
	Large cell neuroendocrine carcinoma		11 (3)
	NSCLC-Not Otherwise Specified		12 (4)
Driver mutation, n (%)	*EGFR* (Epidermal Growth Factor Receptor)		8 (3)
	ALK (Anaplastic Lymphoma Kinase)		4 (1)
	Other / None		157 (50)
	Unknown		146 (46)
UICC stage (TNM 8th edition), n (%)	IIIA		177 (56)
	IIIB		112 (36)
	IIIC		26 (8)
Treatment strategy, n (%)	Curative	Primary surgery with adjuvant therapy	115 (37)
		Neoadjuvant treatment before surgery	109 (35)
		Definitive chemoradiotherapy	53 (17)
	Palliative	Palliative systemic therapy	13 (4)
		Palliative radiotherapy	8 (3)
		Palliative systemic and radiotherapy	3 (1)
		Best supportive care	14 (4)

UICC: Union for International Cancer Control.

Figure 1: *Characteristics of curative treatment in stage III non-small-cell lung cancer (NSCLC).* An overview of patients with stage III NSCLC who underwent treatment with curative intent (n = 277). Details on systemic therapies are provided in appendix figure S2. CRT: chemoradiotherapy; RT: radiation therapy; TKI: tyrosine kinase inhibitor; UICC: Union for International Cancer Control.

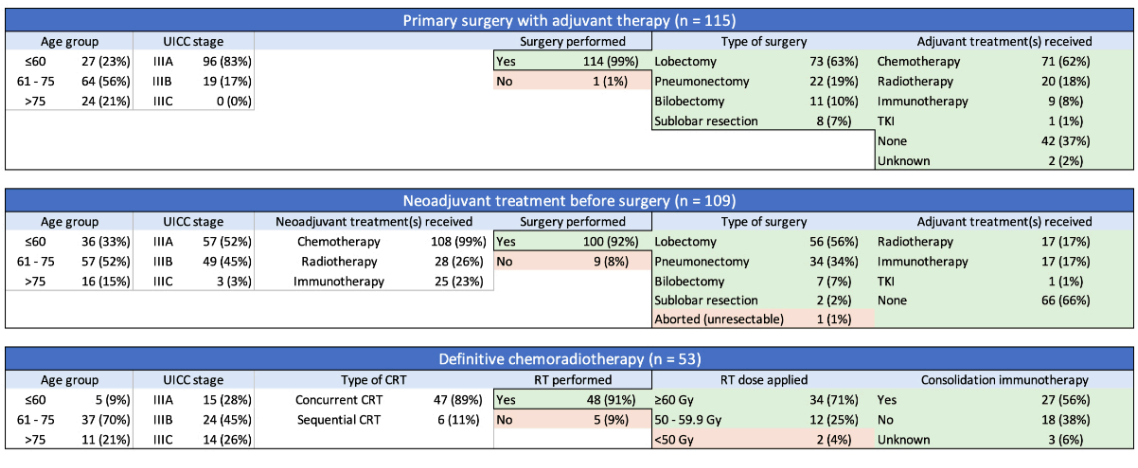


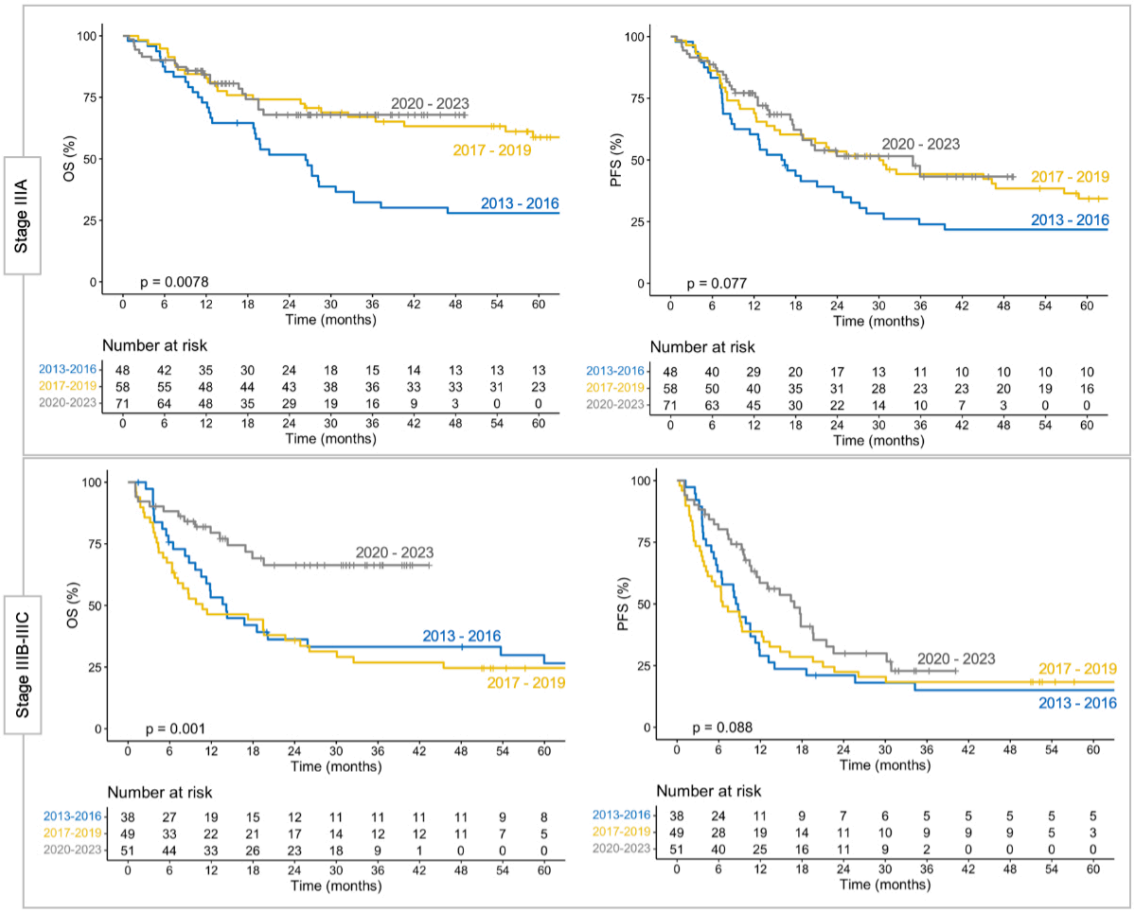
figure S3. Median follow-up was 1.7 years (range: 21 days to 10.6 years). For all patients, median overall survival was 33.3 months (95% confidence interval [CI]: 26.3–63.7), and median progression-free survival was 16.2 months (95% CI: 12.8–19.1). Median overall survival in stage II-IA, IIIB and IIIC was 59.2 months (95% CI: 33.3–NR [upper limit of the 95% confidence interval was not reached]), 19.6 months (95% CI: 11.9–53.8) and 17.9 months (95% CI: 13.6–NR), respectively. Median progression-free survival was 22.8 months (95% CI: 18.0–32.5), 10.6 months (95% CI: 8.8–14.0) and 9.0 months (95% CI: 6.6–21.0) for the respective stages.

For patients diagnosed between 2013 and 2016 (n = 86), the 1-year rates of overall and progression-free survival were 64% (95% CI: 55–76%) and 47% (95% CI: 37–58%), respectively. These rates were 66% (95% CI: 58–76%) and 55% (95% CI: 46–65%) in patients diagnosed between 2017 and 2019 (n = 107), and 82% (95% CI: 76–89%) and 70% (95% CI: 62–78%) in patients diagnosed between 2020 and 2023 (n = 122; p <0.01 for overall survival, p <0.05 for progression-free survival). The Kaplan-Meier estimates of overall and progression-free survival for these different time periods (grouped by disease stages IIIA and IIIB–IIIC) are shown in figure 2.

Patient outcomes separated by treatment strategy are shown in figure 3. In stage IIIA, progression-free survival at 1 and 2 years was 71.6% (95% CI: 63.0–81.2%) and 46.5% (95% CI: 37.2–58.1%) with primary surgery, 77.2% (95% CI: 67.0–88.9%) and 60.0% (95% CI: 47.9–75.2%) with neoadjuvant treatment, and 66.7% (95% CI: 46.6–95.3%) and 50.0% (95% CI: 29.2–85.5%) with definitive chemoradiotherapy. In stages IIIB–IIIC, progression-free survival at 1 and 2 years was 63.2% (95% CI: 44.8–89.0%) and 42.1% (95% CI: 24.9–71.3%) with primary surgery, 51.2% (95% CI: 39.1–66.9%) and 28.4% (95% CI: 18.2–44.3%) with neoadjuvant treatment, and 41.6% (95% CI: 28.4–60.8%) and 25.9% (95% CI: 14.6–45.7%) with definitive chemoradiotherapy. Patients of any stage treated with palliative intent had a poorer prognosis, with a median overall survival of 9.1 months (95% CI: 4.1–19.6) in patients receiving palliative systemic and/or radiotherapy, and 2.4 months (95% CI: 1.6–13.2) with best supportive care.

Disease recurrence was observed in 152 patients (49%). In these patients, the first site(s) of recurrence were locoregional (n = 57; 38%), distant (n = 47; 31%), both locoregional and distant (n = 41; 27%), or new primary lung cancers (n = 7; 5%; with 4 additional new primaries diagnosed in conjunction with locoregional and/or distant recurrence). The rate of locoregional failure at first recurrence (with or without other metastases) was 32% with primary surgery, 28% with neoadjuvant treatment and 34% with definitive chemoradiotherapy (p = 0.78; χ^2). Of all

Figure 2: *Clinical outcomes in stage III non-small-cell lung cancer (NSCLC) during different time periods.* Overall survival (OS) and progression-free survival (PFS) in stage IIIA (upper panels) and stages IIIB–IIIC (lower panels) for patients treated during different time periods. Outcomes appear to have improved in recent years, although confounding factors cannot be excluded.



315 patients, 30 (10%) were diagnosed with brain metastases at any time point (27 at first recurrence).

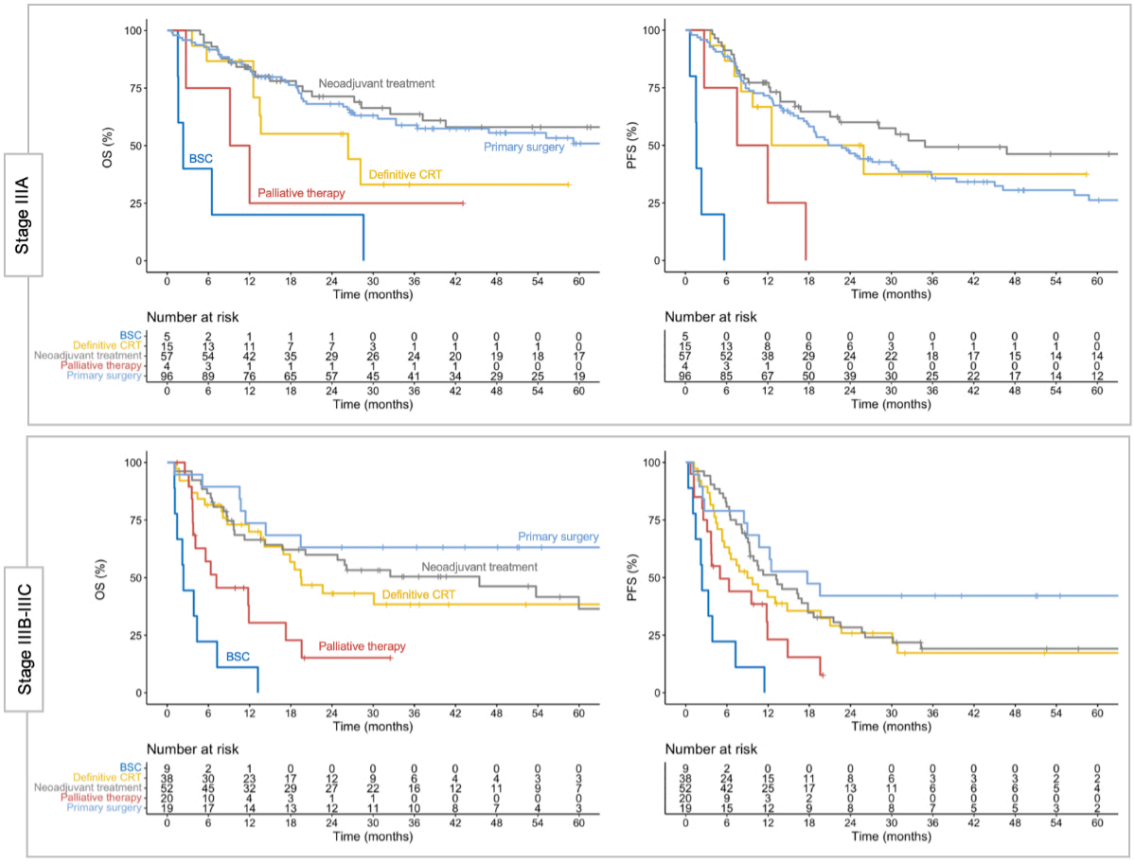
A total of 250 patients were treated with curative intent and followed for at least 2 years. Results of the multivariate Cox regression analysis of progression-free survival performed in this subgroup are shown in figure 4. Age group >75 years (HR: 1.64; p = 0.046) and Union for International Cancer Control (UICC) stage IIIB (HR: 1.71; p = 0.002) were factors associated with an increased risk of progression and/or death following treatment. Other factors did not reach statistical significance in the model.

Discussion

Treatment of stage III non-small-cell lung cancer (NSCLC) has evolved rapidly in recent years. Despite the availability of local and international guidelines, a large heterogeneity in clinical practice persists, reflecting the complexity of multidisciplinary management in these patients [11, 14, 15]. Furthermore, differences in local expertise and expert opinion will affect treatment patterns in the real-world setting. For these reasons, we decided to analyse our institutional experience, both as a method of quality assurance in this challenging setting, and to enhance our understanding of treatment patterns and clinical outcomes in the contemporary era.

In our cohort, a curative treatment approach was pursued in 88% of patients. Although not all patients were able to receive local and/or systemic therapy as initially planned, treatment adherence appeared overall high (figure 1). For example, 91% of patients underwent resection after neoadjuvant treatment. For reference, the rate of definitive surgery was 83% and 75%, respectively, after chemo-immunotherapy and chemotherapy in the landmark CheckMate 816 trial, which also included earlier stages of disease (IB–IIIA) [7]. A relatively high proportion of our patients underwent primary surgery, which included patients without N2 disease, as well as those with unexpected pN2 disease. In definitive chemoradiotherapy, 89% of patients received concurrent treatment, which is preferred over sequential chemoradiotherapy [16]. The rate of patients receiving a radiotherapy dose of ≥60 Gy (71%) was lower than in prospective clinical trials [17, 18]. However, this is explained by the less favourable patient population, which included more elderly patients, and a higher rate of stages IIIB–IIIC (72%), where lower doses were sometimes deemed appropriate. Furthermore, the rate of patients receiving only palliative treatment or best supportive care was 8% and 4%, respectively. This rate was 45% in stage IIIA and 60% in stage IIIB in an analysis of patients treated in the United Kingdom in 2017 [19]. The reason for this discrepancy is likely multi-factorial, including variabilities in clinical practice, which are known to be common in NSCLC [20].

Figure 3: *Clinical outcomes in stage III non-small-cell lung cancer (NSCLC) by treatment strategy.* Clinical outcomes separated by initial treatment strategy for stage IIIA (upper panels) and stages IIIB–IIIC (lower panels). Stage IIIA was most frequently treated with primary surgery, whereas neoadjuvant treatment and definitive chemoradiotherapy (CRT) were more common in stages IIIB–IIIC. Of note, stage IIIC was predominantly treated with definitive chemoradiotherapy, and no patient in that group underwent primary surgery (see figure 1). BSC: best supportive care; OS: overall survival; PFS: progression-free survival.

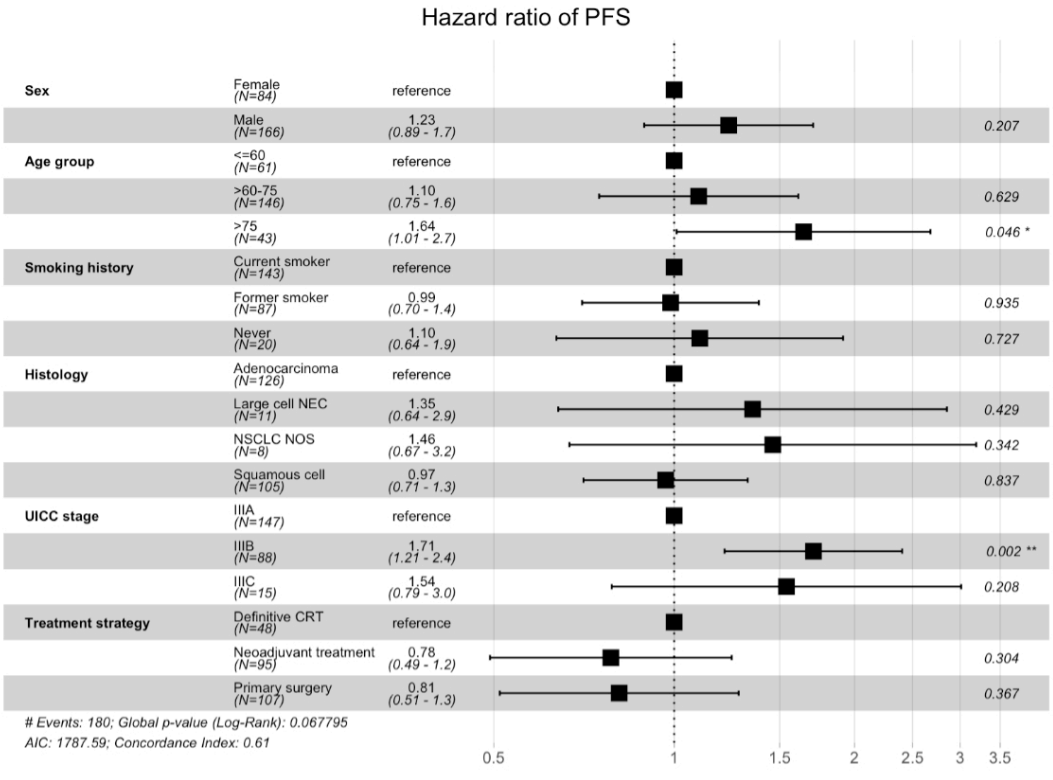


Due to inherent differences, it is difficult to compare treatment outcomes of different clinical trials, as well as real-world cohorts. Similarly, retrospective analyses such as ours are unable to account for all factors that will affect clinical outcomes, including all-cause mortality. This is particularly relevant when comparing surgical approaches and definitive chemoradiotherapy, for which randomised trials have shown similar survival outcomes [21–23]. However, these trials were conducted prior to significant advances in the field, such as the introduction of immune checkpoint inhibitors in both surgical and non-surgical settings [6–9, 24]. In Switzerland, treatment of resectable stage III NSCLC has been notably shaped by clinical trials conducted by the Swiss Group for Clinical Cancer Research (SAKK) [25]. A pooled analysis of four consecutive SAKK trials, which studied different induction regimens in a pre-immunotherapy era, revealed a resection rate of 79% and a median progression-free survival of 12.3 months in 437 patients treated between 1997 and 2016 [26]. Our data compare favourably to these results, with a median progression-free survival of 16.2 months, despite the inclusion of unresectable patients, and some patients receiving palliative care. However, median progression-free survival was not reached in the more recent SAKK 16/14 trial (induction immune checkpoint inhibition), which 7 of our patients participated in [24]. Furthermore, follow-up is generally less rigid in a real-world setting, and underreporting of recurrences is possible in some cases.

Our study has several limitations, including the inherent limitations of any retrospective data analysis, which can be affected by selection bias, unknown confounders and missing data. We cannot exclude that some patients were not presented at the multidisciplinary tumour board. Despite our best efforts, follow-up data was lacking in some patients, and we did not contact external hospitals or caregivers, both due to feasibility and ethical considerations. Our study period also covers a time of significant evolution, and treatment patterns were heterogeneous particularly with regards to systemic therapy. Since e.g. testing for predictive markers was not routinely performed in all patients, we did not conduct additional subgroup analyses at this stage. In the current era, molecular testing is more broadly recommended in stage III NSCLC, as the presence of driver alterations will impact treatment decisions (e.g. regarding consolidation immune checkpoint inhibitors or adjuvant tyrosine kinase inhibitors) [27–29]. Finally, we recognise that our report does not include information on treatment-related toxicities or health-related quality of life. Patient-reported outcome measures are an essential component of modern lung cancer care, and this is currently the subject of other projects at our institution [30].

In conclusion, our long-term institutional analysis in stage III NSCLC revealed that almost 90% of patients underwent treatment with curative intent, including resection in a majority of cases. Rates of treatment completion and survival outcomes were overall encouraging, considering the challenges of lung cancer care in a real-world setting. However, our experience also reflects the need for further improvements, as half of our patients did eventually develop a recurrence. Multidisciplinary care will remain the back-

Figure 4: *Multivariate analysis of progression-free survival (PFS) in stage III non-small-cell lung cancer (NSCLC).* Multivariate Cox regression analysis of progression-free survival in patients treated with curative intent with a minimum follow-up of 2 years (n = 250). Age group >75 years and Union for International Cancer Control (UICC) stage IIIB were associated with a higher risk of progression and/or death. Other factors did not reach statistical significance in the model, although visual trends can be observed. CRT: chemoradiotherapy; NEC: neuroendocrine carcinoma; NOS: not otherwise specified.



bone of lung cancer treatment, which is a field of rapidly increasing complexity. We encourage others to review their clinical experience, as this may have implications for local practice, and contribute to our general understanding of lung cancer care in the real-world setting.

Data sharing statement

De-identified study data may be obtained from the corresponding author upon reasonable request.

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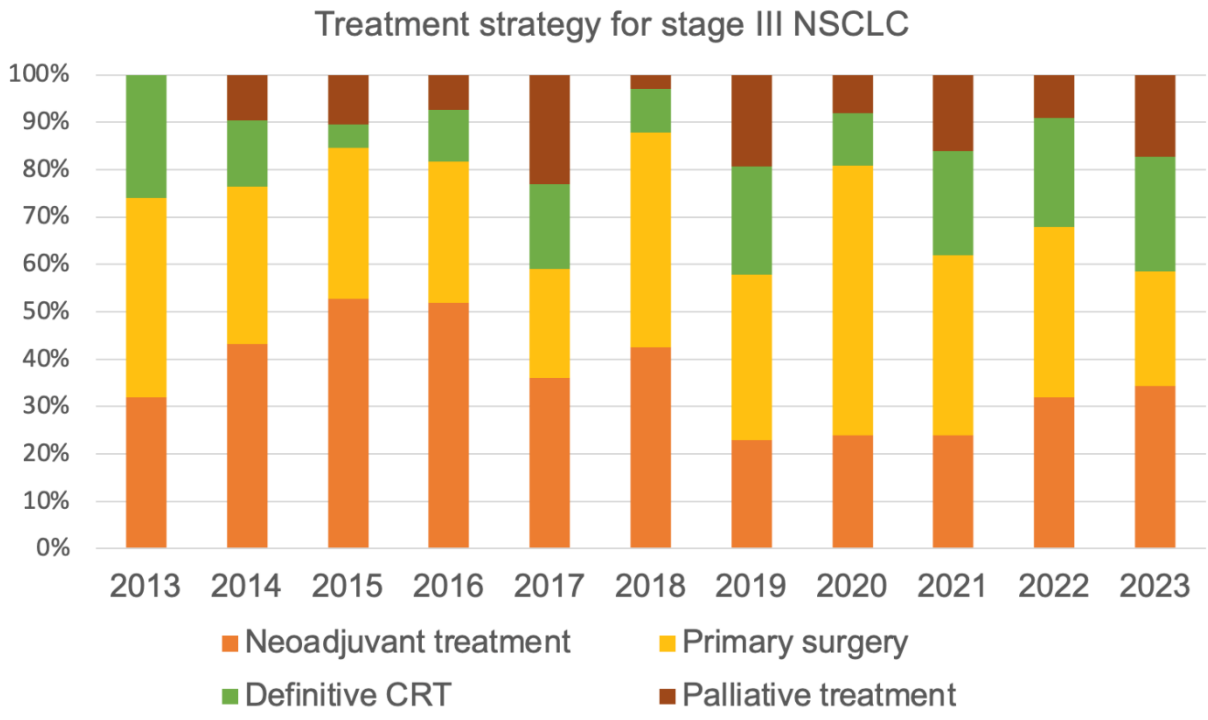
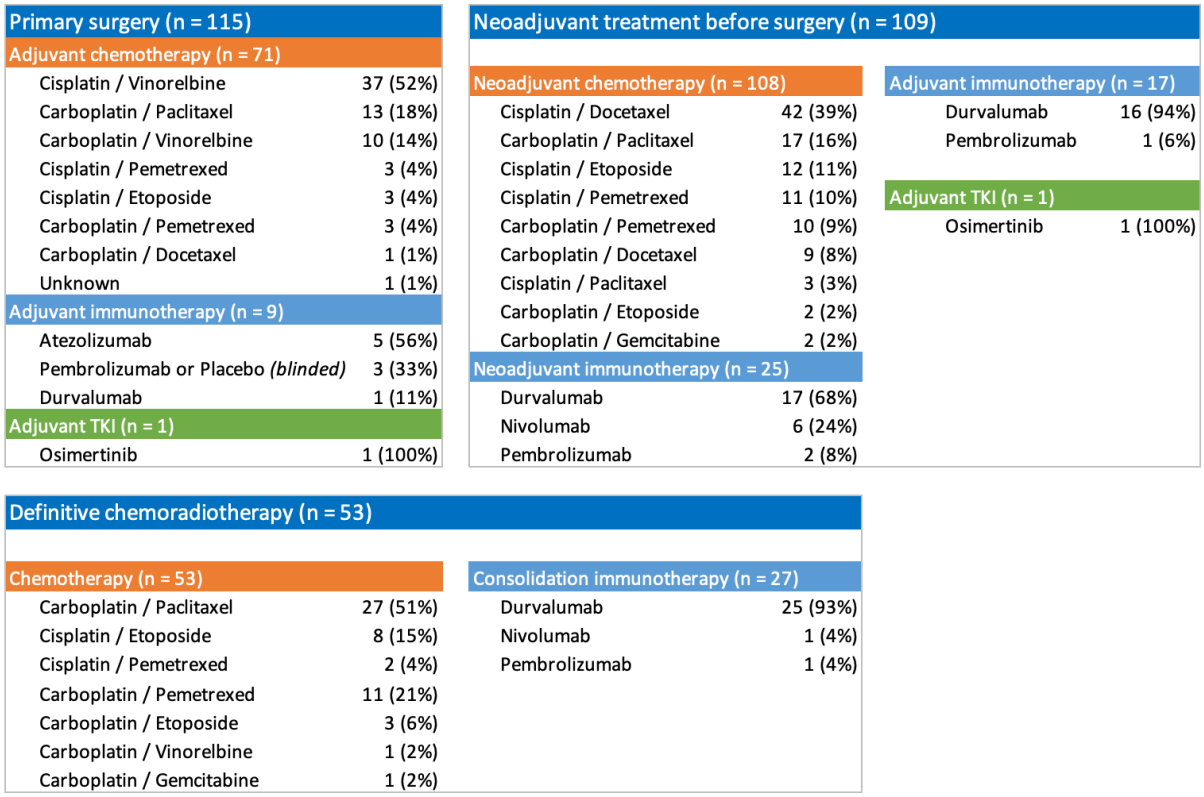
Appendix



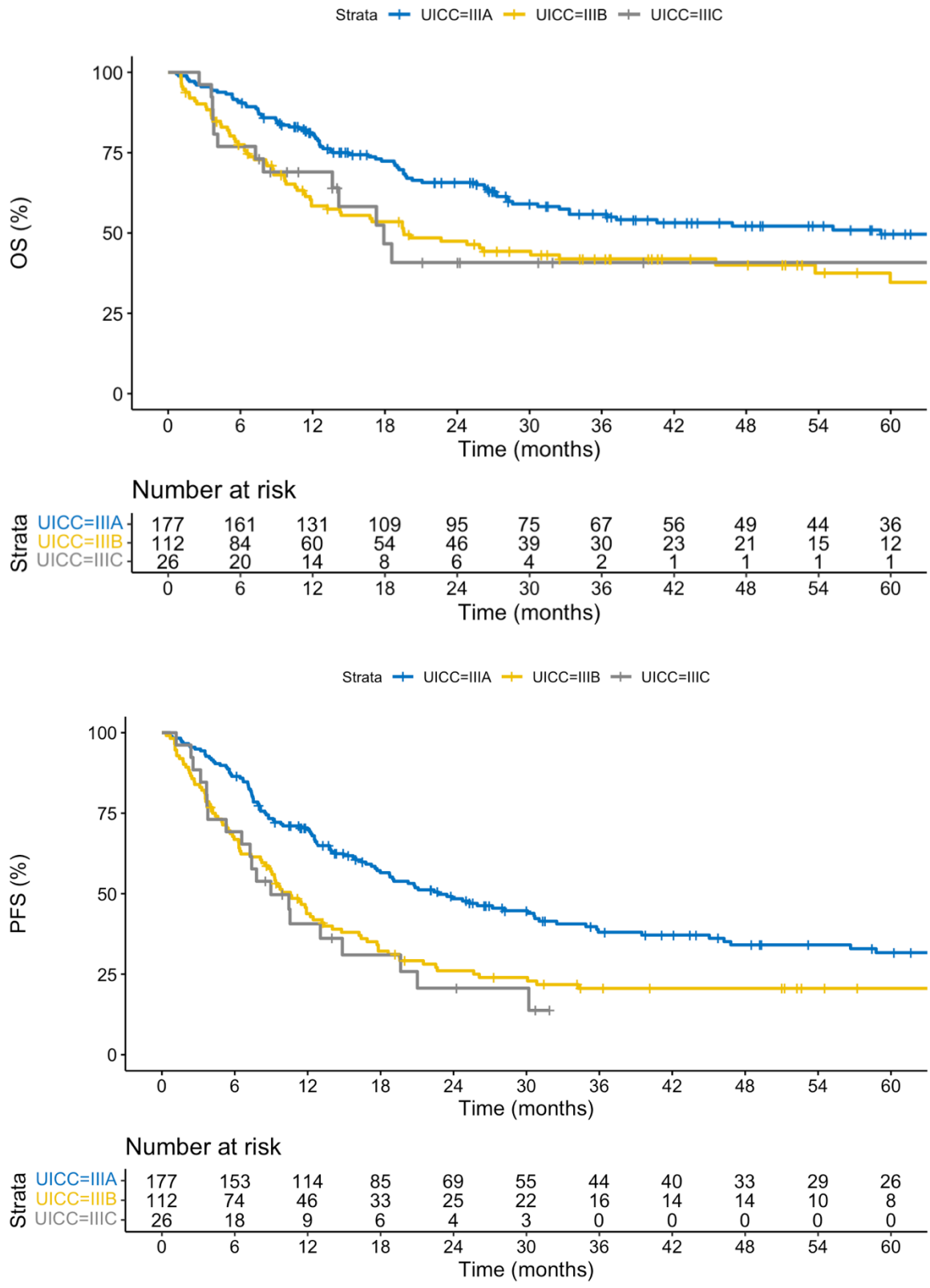
Supplementary Figure 1: Distribution of initial treatment strategies in patients diagnosed with stage III NSCLC between 2013 and 2023.

Abbreviations: CRT, chemoradiotherapy; NSCLC, non-small cell lung cancer.



Supplementary Figure 2: Systemic therapies applied in patients undergoing treatment with curative intent (n = 277).

Abbreviations: TKI, tyrosine kinase inhibitor



Supplementary Figure 3: Overall and progression-free survival separated by disease stage for the entire cohort (n = 315 patients with stage III NSCLC diagnosed between 2013 - 2023).

Abbreviations: NSCLC, non-small cell lung cancer; OS, overall survival; PFS, progression-free survival; UICC, Union for International Cancer Control.