Systematic Review

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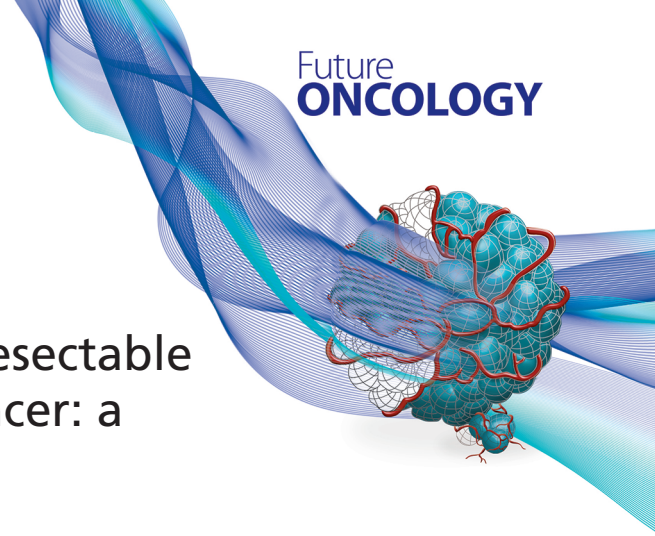

Real-world treatment patterns in resectable (stages I–III) non-small-cell lung cancer: a systematic literature review

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Aim: The aim of this systematic literature review was to describe treatment patterns in nonmetastatic non-small-cell lung cancer. **Methods:** A search was conducted in MEDLINE and EMBASE. Eligible studies were multicentered (>50 patients) and conducted after 2000 in North America, Europe and Asia. **Results:** Twenty studies met the eligibility criteria. Based on US and Canadian studies in the resectable population, the proportion of patients who received neoadjuvant chemotherapy/chemoradiotherapy and adjuvant chemotherapy/chemoradiotherapy increased with increasing stage (i.e., from <3% in stage I to about 40% in stage III and from 15% in stage I to 30% in stage III, respectively). Within the resectable population, the breakdown between bimodal and trimodal therapy was variable, suggesting that clinical practice is not uniform. **Conclusion:** Overall, studies were heterogeneous, precluding data extrapolation across regions. Despite heterogeneity and limited evidence, this review suggested an increase in neoadjuvant and adjuvant chemotherapy with increasing stage, generally in line with treatment guidelines.

Plain language summary: This literature review aimed to describe the treatment patterns in nonmetastatic non-small-cell lung cancer. This review was performed according to the highest methodological standards and searched published and unpublished records of stages I–III non-small-cell lung cancer treatment in North America, Europe and Asia. A limited number of studies were identified showing that in North America treatment with neoadjuvant and adjuvant chemotherapy (with or without radiotherapy) increased with stage. Identified studies in all regions showed that the treatment received, such as bimodal with surgery and chemotherapy compared with trimodal with surgery, chemotherapy and radiotherapy, was quite variable and that practice was not uniform. Overall, the studies were heterogeneous and data could not be extrapolated to practice across all regions. However, the studies suggested an increase in neoadjuvant and adjuvant usage with increasing stage, which is generally in line with treatment guidelines.

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Lung cancer is the leading cause of cancer-related mortality, accounting for almost one in five of all cancer deaths [1]. The majority (80–85%) of lung cancer cases are non-small-cell cancer (NSCLC) [2], with approximately 50% of patients with NSCLC being diagnosed in the nonmetastatic setting [3] and an estimated 20–25% being candidates for surgery [4]. However, prognosis remains poor, with a 5-year overall survival (OS) of 92% in stage IA1, decreasing to 13% in stage IIIC [5].

Clinical practice guideline recommendations for the treatment of resectable NSCLC are based on stage. Surgery is the mainstay of treatment in stages I–II, but it is also recommended in selected patients in stage III. In stages II–III, chemotherapy after surgery is recommended by the European Society for Medical Oncology (ESMO) and National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology (NCCN Guidelines®) [6,7].

While ESMO guidelines specify that adjuvant chemotherapy is preferred over neoadjuvant chemotherapy, NCCN Guidelines® state that neoadjuvant chemotherapy may be a treatment option among patients with stage IIIA (T3, N1) who are candidates for adjuvant chemotherapy. If and to what extent, clinicians and patients adopt these treatment modalities may be determined from published observational studies that capture real-world clinical practice.

The objective of this systematic literature review was to characterize the treatment patterns according to treatment modalities, including the proportion of patients receiving surgery, modality and treatment timing with respect to surgery (i.e., neoadjuvant, adjuvant and peri-operative chemotherapy [CT], chemoradiotherapy [CRT] or radiotherapy [RT]) and the use of specific CT regimens in the real-world treatment of resectable stages I–III NSCLC in North America, Asia and Europe and, in doing so, assess how aligned real-world treatment practice is to published treatment guidelines.

Materials & methods

This systematic literature review was conducted according to the Cochrane collaboration methodology and reported according to Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidance [8,9]. The PRISMA checklist is available in Supplementary Table 1.

Search strategy

Two electronic databases (MEDLINE, EMBASE) were searched on 6 May 2020; abstracts from major oncology and lung cancer conferences were searched either electronically or manually in the previous 2 years. The reference lists of all included articles were hand screened for any additional relevant publications. Authors were contacted when additional information was needed. The search strategies are provided in the supplementary materials (Supplementary Tables 2 & 3).

Eligibility criteria & study selection

Eligibility criteria were pre-specified according to the patient, intervention, comparator and study design (PICOS) framework for evidence-based reviews. Eligible studies included adult patients with resectable (stages I–III) NSCLC in which a breakdown by therapy (e.g., surgery with or without neoadjuvant, adjuvant or peri-operative therapy) was provided. Eligible studies were observational and multi-centered and were conducted after 2000 in Canada, China, France, Germany, Italy, Japan, South Korea, Spain, Taiwan, the UK or the USA. Studies reported in French, German, Italian and Spanish were translated to English and eligible for inclusion; studies in other languages were excluded. Finally, studies with a sample size of 50 or less were excluded (deemed less representative than larger studies). Citations were screened for inclusion by two reviewers; consensus was performed by a third independent reviewer to arbitrate discordant results.

Data abstraction

Data pertaining to study design, patient characteristics and treatment were abstracted. Data were abstracted by one extractor and validated against the primary sources by a second extractor. For each study, the proportion of patients receiving various treatments as well as the proportion of patients receiving further treatment after a first recurrence were calculated. Within-study and across-study temporal trends were abstracted where available.

Assessment of validity

The risk of bias was not assessed due to a lack of an appropriate tool for the type of studies identified in this review. Instead, the internal and external validity of each study's findings related to study population and data source were assessed for each study by two reviewers; conflicts were resolved by a third reviewer. The assessment of external validity was made based on generalizability of the population, sampling frame (including geography or type of practice) and temporal sampling frame (i.e., study period). The internal validity relating to the data source captured the extent and type of missing clinical data. The level of concern was assigned based on exclusions affecting generalizability and was categorized as a concern, some concern and no concern.

Treatment pattern description

Treatment patterns were described within three populations: all patients with stages I–III NSCLC; a subgroup with resected stages I–III NSCLC; and a subgroup of resected patients receiving CT/CRT.

Within studies capturing a full population (i.e., not restricted to resected NSCLC), the proportion of patients receiving surgery was calculated and summarized for each study. Surgery was defined as a procedure in which the lung or part of the lung was surgically resected (thus omitting exploratory thoracotomy).

Within the resected population, treatment was described by three treatment modalities: surgery (with or without RT), neoadjuvant CT/CRT and adjuvant CT/CRT. Peri-operative CT/CRT was described separately on a study basis, since this was reported in only a few studies. Neoadjuvant therapy was defined as therapy administered prior to surgery. Adjuvant therapy was defined as therapy administered after surgery. Peri-operative therapy was defined as therapy administered both prior to and after surgery. Treatment was defined as bimodal when it included surgery and CT and defined as trimodal when it included surgery, CT and RT. The proportion of patients receiving each modality, among all resected patients, was calculated and presented for each study.

In terms of CT regimens, the proportion of patients receiving each regimen, among all resected or potentially resectable patients who received CT or CRT was summarized. Treatment patterns were presented by stage and country. The data were not pooled or meta-analyzed due to heterogeneous study designs, objectives and reporting.

Results

In total, 8107 records were screened for eligibility, 169 full-text records were reviewed and 20 publications from 20 unique studies were included in this review (Figure 1).

Of the 20 studies, ten were conducted in North America, four in Europe and six in Asia (Table 1). All studies were retrospective, except for the study by Pinquié *et al.*, which was prospective with a retrospective component (to collect information on treatment administered prior to study start) [10].

Nine studies were conducted using databases or registries, three in North America [11–13], three in Europe [10,14,15] and three in Asia [16–18]. Seven regional studies were described as population based [19–25], with none at the national level. One study only included community care centers in southern states of the USA [26], two studies were small in size (<100 patients) [27,28] and one included only two hospitals [29].

Eligibility criteria varied across studies, particularly regarding the exclusion of certain patients (Table 1). These exclusions pertained to patients with specific types of surgeries (e.g., segmentectomy and wedge resection) [11,17,27], the extent of resections (e.g., incomplete resection R1 and R2) [12,15,17,18,28], treatment types (e.g., RT or surgery alone) [14,28] and modalities (e.g., neoadjuvant CT/CRT) [17,20,27]. These restrictions limited the authors' ability to make comparisons within similarly defined populations.

Disease stage varied across studies, with a majority of studies capturing stage III NSCLC [14,16,17,21,24,27]. Four studies included stage IV but provided separate reporting for stages I–III (Table 1).

Surgery

Of the nine studies that included resected and unresectable NSCLC (see Table 1), two large studies conducted in France and the USA allowed the proportions of resected stages I–III (stages IIIA and IIIB) NSCLC to be estimated at 50.3% and 38.1%, respectively (Table 2) [10,11].

The proportion of nonmetastatic patients receiving surgery tended to decrease with an increase in stage. In six studies that described treatment in stages I–III NSCLC among those receiving surgery, definitive RT or non-curative treatments (Table 2), the proportions of patients receiving surgery ranged from 68.2 to 78.6% in stage I [11,13], 45.5 to 45.8% in stage II [11,23] and 10.3 to 17.5% in stage III [11,19,21].

In four studies that described treatment among those treated with surgery or definitive RT (and thus excluded those who received no treatment or non-curative-intent treatment; Table 2), the proportions of patients receiving surgery were 94% in stage I [22] and 86.6% in stage II [22] and ranged from 20.8 to 59% in stage III [14,22,24].

Neoadjuvant, adjuvant, peri-operative therapies by stage

Stages I–III

Nine studies reported on the use of CT, CRT and RT in stages I–IIIA NSCLC [10–12,15,20,22,26,28,29]. Three studies conducted in France and the USA (two studies) were considered comparable and described the treatment patterns in the resected population (Table 3) [11,12,29]. Across those three studies, 9.2–24.6% received neoadjuvant CT/CRT prior to surgery, 24.2–28.3% received adjuvant CT/CRT following surgery, and 51.2–62.6% underwent surgery alone (with or without RT). The remaining six studies were not considered comparable due to missing modalities (i.e., neoadjuvant CT/CRT or surgery) and a lack of information on the timing of CT/CRT. Among those six,

Table 1. Summary of study and patient characteristics across the 20 included studies.

Author (year)	Countries	Data source	Study period	Eligible population	PS	Stage‡	Resected, n
North America							
Arnold (2016)	USA	NCDB tumor registry, hospital-based, approximately 30% of hospitals nationwide	2003–2009	Diagnosis§	–	I–IV	45,933
Buck (2015)	USA	Vector Oncology Data Warehouse, EMR/claims, community oncology practices in southern and midwestern US	2007–2013	Surgical resection††	–	IB–IIIA	609
Gould (2017)	USA	KPSC tumor registry, primary care and cancer specialists (14 hospitals) and >200 medical practices; considered population based	2008–2013	Diagnosis	–	0–IV	1533
Rajaram (2016)	USA	NCDB tumor registry, hospital-based, approximately 30% of hospitals nationwide	2002–2011	Complete surgical resection (R0)	–	IB–IIIA	112,049
Valle (2016)	USA	NCCN Oncology Outcomes Database, eight institutions nationwide	2007–2011	Diagnosis	–	I	1183
Booth (2012)	Canada	The Ontario Cancer Registry, population based, regional	2004–2006	Surgical resection†,¶	–	I–IV	3354
Moore (2019)	Canada	BC Cancer Agency, population based, regional	2005–2012	Diagnosis	0–4	III	133
Moore (2020)	Canada	BC Cancer Agency, population based, regional	2005–2012	Diagnosis	0–4	II	245
Ramsden (2015)	Canada	BC Cancer Agency, population based, regional	2005–2010	Surgical resection	0–4	II	258
Vinod (2012)	Canada	BC Cancer Agency database, population based, regional	2000–2007	Diagnosis	0–4	IIIA–IIIB	250
Europe							
Pinquié (2017)	France	ESCAP-2011-CPHG database, 53 hospitals across France#	2010	Diagnosis	0–4	0–IV	741
Riquet (2012)	France	Thoracic Surgery hospital database, two hospitals	2001–2006	Surgical resection	–	I–IIIA	1195
Couñago (2018)	Spain	Medical records, 15 hospitals nationwide	2005–2014	Diagnosis, potentially resectable§§	–	IIIA N2	118
Chouaid (2018)	EU3	Medical records, 39 hospitals in France, Germany and the UK	2009–2011	Complete surgical resection (R0)	–	IB–IIIA	831
Asia							
Maniwa (2018)	Japan	Thoracic Surgery Study Group of Osaka University, 12 hospitals	2006–2013	Surgical resection†	–	III	94
Sonobe (2013)	Japan	Japan-Multinational Trial Organization, 25 hospitals, nationwide	2000–2004	Complete surgical resection (R0)‡‡,†,¶	0–1	IIIA N2	496
Yoh (2019)	Japan	Medical records, 34 hospitals, nationwide	2008–2013	Complete surgical resection (R0)	–	I	5006
Fan (2015)	China	Shanghai Health Information Network, population based	2011–2013	Diagnosis	–	I–IV	5069
Lin (2017)	Taiwan	Taiwan Cancer Registry, claims data, nationwide	2002–2012	Surgical resection	–	III N2	558
Lee (2013)	Korea	Hallym University Medical Center, five hospitals	2000–2011	Complete surgical resection (R0)¶¶	–	IA–IIIA	93

†Patients who had received neoadjuvant CT were ineligible to participate in the study.
‡Pathological or clinical stage. In studies where the population was surgically resected and where both clinical and pathological stage were reported, pathological stage was chosen for reporting in this table.
§Patients who received adjuvant RT without CT were excluded. Also among those resected, patients with positive margins (i.e., R1 and R2) were excluded.
¶Patients who received neoadjuvant RT were excluded.
#ESCAP-2011-CPHG cohort is a subset of the KBP-2010-CPHG cohort, which includes data from 104 centers with a pneumology department. Authors reported that there were no significant differences between the two cohorts based on age, sex, weight, height, BMI, smoking status, performance status, histology and stage at diagnosis.
††Excluded wedge resection and segmentectomy.
‡‡Only included lobectomy, bilobectomy and pneumonectomy.
§§To be eligible, patients had to have been treated with CT/CRT either as neoadjuvant CT/CRT or definitive CT/CRT.
¶¶To be eligible, patients had to have been treated with CT either as neoadjuvant CT, peri-adjuvant CT or adjuvant CT.
CRT: Chemoradiotherapy; CT: Chemotherapy; EMR: Electronic Medical Records; EU3: France, Germany and the UK; KPSC: Kaiser Permanente Southern California; NCDB: National Cancer Data Base; NCCN: National Comprehensive Cancer Network; PS: Performance status.

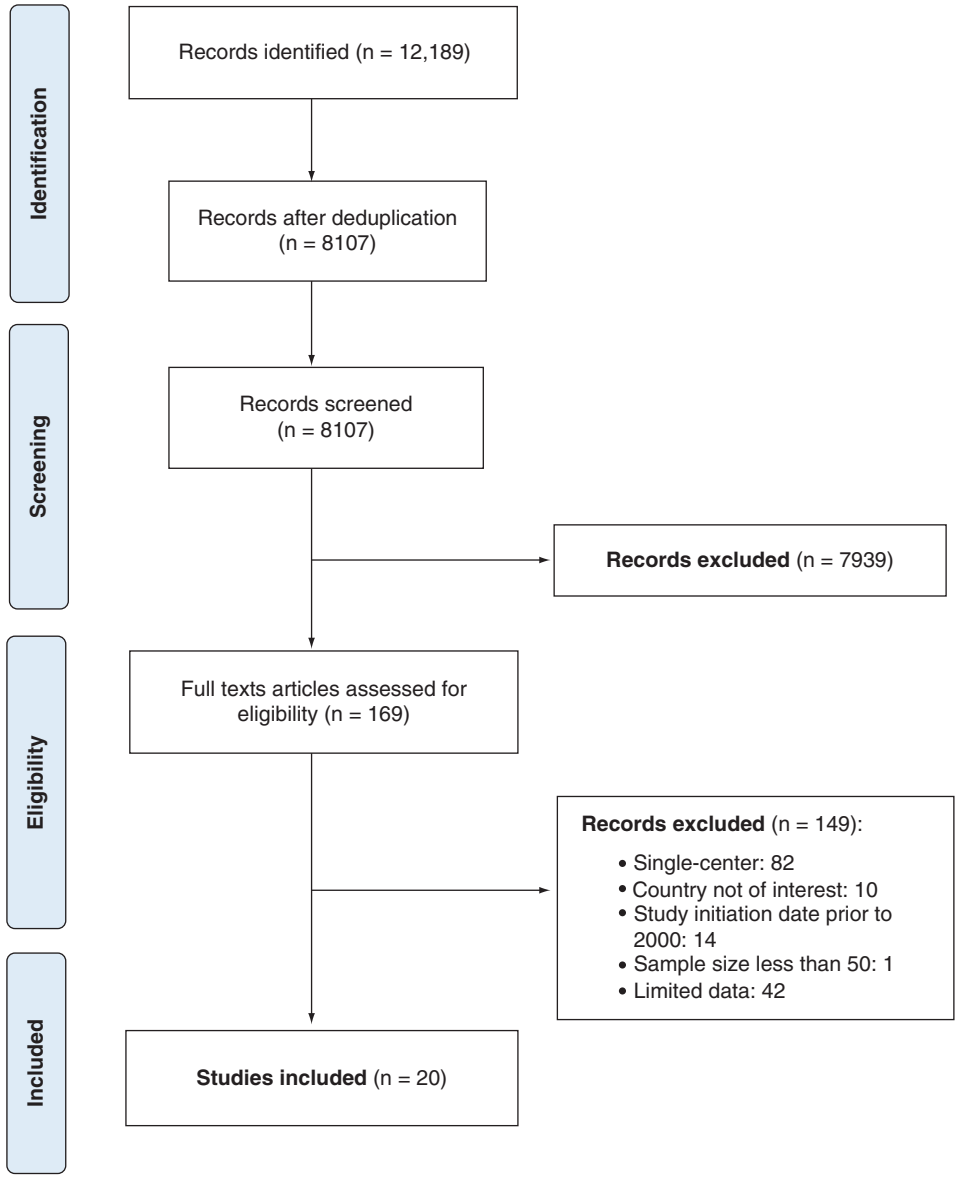

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) diagram. The search was conducted for multiple objectives (including treatment patterns). It included search of the Cochrane Central Register of Controlled Trials, and records retrieved from Cochrane Central Register of Controlled Trials are included in the total records identified.

one study in Korea reported on the peri-operative setting, indicating that 7.8% received neoadjuvant CT, 9.8% received peri-operative CT and 82.4% received adjuvant CT [28].

Stage III

Thirteen studies reported on the use of CT, CRT and RT in stage III NSCLC [10,11,14–17,19–22,24,26,27]. Three studies conducted in Canada and the USA were comparable and described the treatment patterns in the resected population (Table 3) [11,21,24]. Arnold *et al.* and Moore *et al.* reported that 37 and 44% received neoadjuvant CT/CRT, 28.6 and 33.8% received adjuvant CT/CRT and 34.4 and 21.8% underwent surgery alone (with or without RT), respectively [11,24]. The study of Vinod *et al.* used the same data source but at an earlier time, and therefore it was superseded by Moore *et al.* [21,24]. The remaining ten studies were not considered comparable due to some modalities not being reported (i.e., neoadjuvant therapy or surgery) [14–17,20,26,27] or timing not being reported [10,19,22].

Table 2. Proportion of resected patients among stages I–III non-small-cell lung cancer.

Study (year)	Stage	Country	Study period	Total (n)	Resected	
					n	%
Population receiving surgery, definitive RT# or non-curative Tx†						
Valle (2016)	I	USA	2007–2011	1506	1183	78.6
Arnold (2016)	I	USA	2003–2009	53,088	34,307	64.6
Arnold (2016)	II	USA	2003–2009	11,874	5407	45.5
Moore (2020)	II	Canada	2005–2012	535	245	45.8
Gould (2017)	III	USA	2008–2013	1382	242	17.5
Arnold (2016)	III	USA	2003–2009	53,705	5514	10.3
Vinod (2012)	III	Canada	2000–2007	2153	250	11.6
Gould (2017)	0–II	USA	2008–2013	1734	1291	74.5
Arnold (2016)	I–III§	USA	2003–2009	118,667	45,228	38.1
Pinquié (2017)	I–III¶	France	2010	1386	697	50.3
Population receiving surgery or definitive RT#						
Fan (2015)‡	I	China	2011–2013	912	857	94.0
Fan (2015)	II	China	2011–2013	292	253	86.6
Moore (2019)	III	Canada	2005–2012	638	133	20.8
Fan (2015)	IIIa	China	2011–2013	659	389	59.0
Couñago (2018)	IIIa	Spain	2005–2014	247	118	47.8
Fan (2015)	I–III	China	2011–2013	1863	1489	79.9

†Non-curative Tx typically included palliative chemotherapy +/- RT, palliative RT, best supportive care or no active treatment.
‡Unclear if treatment with non-curative intent was included in the denominator or not.
§Number and proportions were calculated based on digitized proportions derived from Figure 4 in Arnold *et al.* and number of patients per stage in Table 1 of Arnold *et al.*
¶Authors reported that the proportions of patients receiving surgery among stages 0–IV was 741/3418 (21.7%). Based on the data by stage reported by the authors, the number and percentage of patients receiving surgery among all patients with stages I–III was estimated at 697/1386 (50.3%).
#It was not always clear whether RT was definitive or/and palliative.
RT: Radiotherapy; Tx: Treatment.

Stages I, II & III

Six studies described the treatment patterns in resected patients by stage (Table 3). The study of Arnold *et al.* was the only one that provided stage-specific proportions across stages I, II and III [11]. Within this study, the proportion of patients receiving neoadjuvant CT/CRT tended to increase with increasing stage, from 2.5% in stage I to 14.2% in stage II and 37.0% in stage III. The proportions using adjuvant therapy were 14.1% in stage I, 35.2% in stage II and 28.6% in stage III. Conversely, the proportion of patients receiving surgery alone (with or without RT) tended to decrease with increasing stage (83.4% in stage I, 50.6% in stage II and 34.4% in stage III). In the adjuvant setting, there tended to be an increase between stages I and II (from 14.1% to 35.2%) and then possibly a slight decrease in stage III (28.6%). These patterns were corroborated by across-study comparisons showing similar trends.

Peri-operative therapy was reported in three studies [14,21,28], with one study reporting that 0.8% of resected patients received peri-operative RT [21] and the other two studies reporting that between 10 and 52% of resected patients received peri-operative CT, CRT or RT. The two later studies, unlike the study of Vinod *et al.*, excluded patients receiving surgery alone or with RT (see footnote of Table 1 for details of inclusion criteria) [14,28].

Additionally, the authors identified four studies that reported the proportions of patients receiving the different modalities irrespective of timing [10,16,17,19]. In the three most recent studies, the studies reported that about 30–33% of patients received surgery (with or without RT) in stage III resected NSCLC [10,16,19]. Treatment of the remaining patients was split between bimodal and trimodal therapy with no clear pattern (see Supplementary Table 4).

CT regimens

The CT regimens used alongside surgery are provided in Figure 2, with nine studies providing a breakdown by regimen in the adjuvant setting [10,15,17,18,20,25–28] and one study reporting separately in the neoadjuvant setting [10].

In one study in the USA, carboplatin-paclitaxel was the most common adjuvant regimen (30%), followed by cisplatin monotherapy (14%) [26]. In two studies in Canada, cisplatin-based regimens were more common,

Table 3. Proportion of patients by treatment modality (with timing) in resected stages I–III non-small-cell lung cancer.

Study (year)	Country	Study period	Total (n)	Patients, n (%)					
				S (±RT)		Neo-CT/CRT		Adj-CT/CRT	
				n	%	n	%	n	%
Stage I									
Arnold (2016)	USA	2003–2009	4293	3581	83.4†	108	2.5‡	604	14.1‡
Rajaram (2016)	USA	2002–2011	55,016	44,563	81.0 §	1540	2.8‡,¶	8913	16.2‡
Stage II									
Arnold (2016)	USA	2003–2009	5407	2737	50.6†	766	14.2‡	1904	35.2‡
Moore (2020)	Canada	2005–2012	245	112	45.7 §	7	2.9‡	126	51.4‡
Stage III									
Arnold (2016)	USA	2003–2009	5547	1909	34.4†	2,053	37.0‡	1585	28.6‡
Moore (2019)	Canada	2005–2012	133	29	21.8#	59	44.4‡‡	45	33.8‡‡
Vinod (2012)	Canada	2000–2007	250	148	59.2§	34	13.6‡,††	68	27.2‡,††
Stages I–III									
Riquet (2012)	France	2001–2006	1195	612	51.2§	295	24.6§§	289	24.2§§
Arnold (2016)	USA	2003–2009	15,247	8227	54.0†	2927	19.2‡	4093	26.8‡
Rajaram (2016)	USA	2002–2011	112,049	70,031	62.6§	10,308	9.2‡,¶	31,710	28.3‡
Stages II–III									
Rajaram (2016)	USA	2002–2011	57,033	25,468	44.7§	8768	15.4‡,¶	22,797	40.1‡

†Includes patients who received RT before surgery, but study excluded patients who received post-operative RT without CT.
‡Includes those who received CT with RT.
§Includes pre- and post-operative RT.
¶Patients who received CT pre-operatively and post-operatively were included in the neoadjuvant therapy group.
#Includes those patients who received RT alone post-operatively.
††Among 34/250 neo-CT/CRT, there were four (1.6%) neo-CT and 30 (12.0%) neo-CRT; among the 68 who received adj-CT/CRT, there were 62 (24.8%) adj-CT and six (2.4%) adj-CRT.
‡‡Among 59/133 neo-CT/CRT, there were six (4.5%) neo-CT and 53 (39.8%) neo-CRT; among the 45 who received adj-CT/CRT, there were 38 (28.6%) adj-CT and seven (5.3%) adj-CRT.
§§Among 295/1195 neo-CT/CRT, there were 244 (20.4%) neo-CT and 50 (4.2%) neo-CRT; among the 289 who received adj-CT/CRT, there were 204 (17.1%) adj-CT and 85 (7.1%) adj-CRT.
¶¶Among 3615/45,933 neo-CT/CRT, there were 1767 (3.8%) neo-CT and 1848 (4.0%) neo-CRT; among the 7791 who received adj-CT/CRT, there were 6851 (14.9%) adj-CT and 940 (2.0%) adj-CRT.
Adj: Adjuvant; CRT: Chemoradiotherapy; CT: Chemotherapy; Neo: Neoadjuvant; RT: Radiotherapy; S: Surgery.

with some regional and/or temporal differences (e.g., cisplatin-gemcitabine was most common [80%] in British Columbia [2005–2010; stage II], whereas cisplatin-vinorelbine was most common [71%] in Ontario [2004–2006; stages 0–IV]) [20,25].

In two studies in Europe, platinum-vinorelbine was the most common regimen in the adjuvant setting (36% [15]–60% [10]). Chouaid *et al.* provided a breakdown by platinum agent; cisplatin-vinorelbine was the most commonly used treatment (ranging from 56% in Germany to 73% in the UK) [15]. In the neoadjuvant setting, Pinquié *et al.* reported that platinum-vinorelbine (31%), platinum-pemetrexed (21%) and platinum-gemcitabine (21%) were the three most common regimens but did not provide a further breakdown by platinum agent [10].

In Japan, a tegafur-uracil combination (UFT) was used in nearly all stage I patients (92.9%) in one adjuvant study [18] and in about a quarter of stage III patients (28.7%) in another adjuvant study [17]. Platinum-based CT was the most common CT in stage III in Japan (64.5–71.3%) [17,27]. In a study in South Korea, cisplatin-vinorelbine (39.8%), cisplatin-gemcitabine (15.1%) and carboplatin-vinorelbine (14.0%) were the most common adjuvant therapies [28].

Treatment sequencing after first recurrence

Information on treatment sequencing after a first recurrence was provided by four studies [10,15,23,26]. The study by Pinquié *et al.* was the only one to specifically report treatment modalities after a first recurrence [10]. Within the follow-up period of up to 2 years post-diagnosis, 31% of the resected population had gone on to receive subsequent treatment [10]. Among those receiving a second treatment, the most common modality for the second treatment was CT alone (45%), with only 7.8% of patients receiving a second surgery (alone or with CT, CRT or RT) [10].

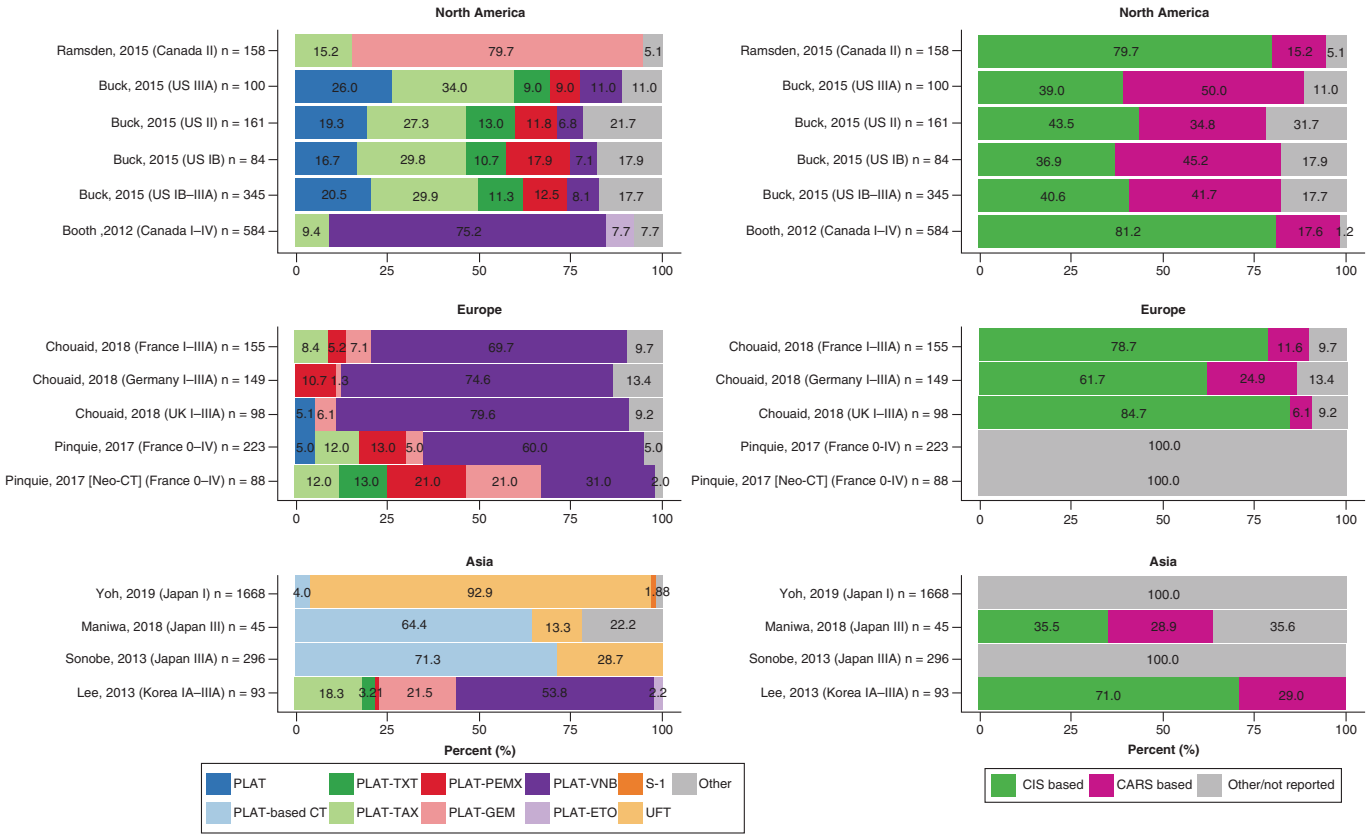

Figure 2. Neoadjuvant and adjuvant chemotherapy regimens in North America, Europe and Asia. All studies reported the CT regimen in the adjuvant setting only, except for the study of Pinquié *et al.*, which also reported the details of the regimens in the NEO setting. Additionally, in the study of Lee *et al.*, the CT regimens might include NEO, adjuvant and peri-operative. In studies that reported the nature of the PLAT agent (i.e., all studies except Pinquié *et al.*), PLAT alone was either *CIS* or CARB.
CARB: Carboplatin; *CIS*: Cisplatin; CT: Chemotherapy; ETO: Etoposide; GEM: Gemcitabine; NEO: Neoadjuvant; PEMX: Pemetrexed; PLAT: Platinum; S-1: Tegafur, gimeracil and oteracil; TAX: Paclitaxel; TXT: Docetaxel; VNB: Vinorelbine; UFT: Tegafur-uracil.

There was no apparent major difference by stage (i.e., CT alone: 46% in stages 0–IIB vs 42% stage IIIA, second surgery [alone or with CT, CRT or RT]: 9.6% in stages 0–IIB vs 5.6% in stage IIIA) [10].

Two other studies reported on the proportions of the resected population receiving subsequent systemic therapy after a recurrence: 27% in Moore *et al.* (follow-up 10 years) and 50% in Chouaid *et al.* (follow-up 4.6 years) [15,23]. Finally, Buck *et al.* reported on specific treatment regimens, stating that carboplatin-paclitaxel, erlotinib and pemetrexed were the top three most common regimens after disease recurrence [26].

Temporal trends

Within-study temporal trends were available from two studies [12,29]. From 1995–2000 to 2001–2006, Riquet *et al.* reported an increase in the use of both neoadjuvant CT/CRT and adjuvant CT/CRT and a coinciding decrease in surgery (with or without RT) in stages I–III (neoadjuvant CT/CRT: 11.8–24.6%; adjuvant CT/CRT: 16.3–24.2%; surgery: 71.9–51.2%, respectively) [29]. Similarly from 2002 to 2011, Rajaram *et al.* reported increasing trends in the use of neoadjuvant and adjuvant CT/CRT and decreasing trends in surgery (with or without RT) use in stages II–III (neoadjuvant CT/CRT: 11.2–14.8%; adjuvant CT/CRT: 18–43.5%; surgery: 70.8–41.7%) [12].

Between-study temporal trends were available from two studies that used the British Columbia Cancer Agency database and had similar eligibility criteria; they showed that the proportion of patients receiving neoadjuvant CT/CRT was greater in the more recent study (2005–2012) compared with the older study (2000–2007; i.e., 44.4 vs 13.6%, respectively) [21,24].

Assessment of validity

The validity assessment contained some level of concern about generalizability in each study (see Supplementary Table 5). There was concern about the generalizability of the eligible population in ten or more studies in each category assessed. In particular, the study period was found to be of some concern because all studies were at least 6 years old, and thus there might have been some evolution in treatment practices. There was no major concern about data sources; thus, information bias was assessed as being low overall.

Discussion

To the authors' knowledge, this is the first systematic literature review of the treatment patterns in resectable NSCLC in North America, Europe and Asia. There was a limited number of multicenter studies that reported the full breakdown of therapies, and within the available evidence, there was little information on the CT regimens used in the neoadjuvant setting.

Within the overall stages I–III NSCLC population that included both resected and unresectable patients, the authors observed that approximately 40–50% underwent surgical resection [10,11]. Surgical intervention was most common in stage I, with over two-thirds of patients receiving surgery, and was least frequent in stages IIIA/B, where it was received by around 10–20% of patients. This trend is perhaps unsurprising, given that one of the main considerations in selecting patients for surgical resection is lymph node involvement status, which by definition is absent in stages I and IIA and is present in TNM stage IIIB [6,7,30].

Within the surgically resected population of the USA- and Canada-based studies, adjuvant CT (with or without RT) was most commonly used in stages II and III, and neoadjuvant CT was most commonly used in stage III. In fact, in stage III disease, neoadjuvant CT usage with or without RT was often more common than an adjuvant modality, with temporal trends showing greater uptake of neoadjuvant CT and CRT use in stage III in more recent years [12,21,24]. These findings are generally consistent with the latest NCCN Guidelines® recommending that adjuvant CT be used primarily in stages IIB–III and that patients who are candidates for adjuvant CT in stage IIIA (T1–3, N0–1) may be treated with neoadjuvant CT as an alternative option [6,7].

In Europe and Asia, there was less evidence in regard to neoadjuvant and adjuvant therapy use, although some information was available on treatment modalities (i.e., surgery and bimodal and trimodal treatment) [16,17]. The one European study that did report on neoadjuvant therapy reported increasing trends in its use, with a quarter of resected stage I–III patients receiving neoadjuvant RT/CT/CRT in 2001–2006 [29]; however, this was based on data from just two hospital centers in France, and therefore it was difficult to determine if this generalizes to other centers in France or elsewhere in Europe. Furthermore, it is unclear whether this trend of increased use continued, given the current recommendation by ESMO that aside from a potential benefit of downstaging via neoadjuvant therapy, adjuvant therapy is preferred over neoadjuvant therapy [7].

In terms of CT regimens, there were some notable differences between regions. Cisplatin was the most common platinum agent used in doublet combinations in Canada, France, Germany and the UK, in line with the ESMO guidelines stating that cisplatin is preferred [7]. However, in the USA, both carboplatin and cisplatin were used by a large proportion of the population [26] and in line with the NCCN Guidelines® recommending both platinum agents. UFT use was exclusive to the Japan-based studies. Consistent with Japanese recommendations, UFT was the most common regimen used in stage I [18,31] and was evident in the treatment of stage III disease.

Despite the broad scope of this review and alignment with good practice guidelines, there are several limitations. First, the generalizability of the results may have been impacted by the absence of national population-based studies; although national studies were included, they tended to include mostly academic, teaching or specialized cancer centers, which have been associated with different patterns of care than community settings [12,32,33]. Applicability to current clinical practice may also have been limited due to study periods spanning the range from 2000 to 2014. However, temporal trends both within and between studies elucidated the evolution in treatment during that time, and since 2014 there have been no major approvals or changes in the guideline recommendations for the treatment of resectable NSCLC. In view of two novel immunotherapies showing positive results in the neoadjuvant and adjuvant settings after many years of limited innovation in this space [34,35], this review may help establish a 'baseline' from which the treatment of resectable NSCLC will evolve. Finally, the eligibility criteria of certain studies (e.g., exclusion of certain systemic treatments, RT or surgery types) limited the authors' ability to obtain and compare the complete treatment patterns in resectable NSCLC across studies. Overall, the studies were heterogeneous and the treatment patterns in the neoadjuvant, adjuvant and peri-operative settings could only be

determined in subsets of studies; however, these subsets are useful in understanding contemporary treatments and historic trends in the treatment of resectable NSCLC.

Conclusion

To our knowledge, this is the first systematic literature review describing the real-world treatment patterns in stages I–III resectable NSCLC. Although a limited number of studies were available and the studies were heterogeneous, the review suggested an increase in neoadjuvant and adjuvant CT use with increasing stage, generally in line with guidelines. Additional real-world studies will be needed to fill the gaps in our understanding of the relative use of neoadjuvant, adjuvant and peri-operative therapy as well as CT regimens used in resectable NSCLC.

Summary points

- To the authors' knowledge, this is the first systematic literature review performed to describe treatment patterns in resectable non-small-cell lung cancer (NSCLC) prior to the introduction of immunotherapies in this therapeutic space.
- Neoadjuvant and adjuvant chemotherapy (with or without radiotherapy) use increases with stage, while the use of surgery alone or with radiotherapy decreases with increasing stage in stages I–III resectable NSCLC.
- Neoadjuvant chemotherapy use with or without radiotherapy was often more common than adjuvant chemotherapy in stage III NSCLC.
- The findings were generally consistent with the NCCN Guidelines® recommending that adjuvant chemotherapy be used primarily in stages IIB–III and that patients who are candidates for adjuvant chemotherapy in stage IIIA (T1–3, N0–1) may be treated with neoadjuvant chemotherapy as an alternative option.
- Cisplatin use was highest in Europe, Canada and Asia; in the USA, carboplatin use was more common.
- In terms of temporal trends, there was an increase in neoadjuvant and adjuvant chemotherapy (with or without radiotherapy) use in all stages combined between the late 1990s and the early 2000s.
- Overall, studies were heterogeneous and the treatment patterns in the neoadjuvant, adjuvant and peri-operative settings could only be determined in subsets of studies; however, these subsets are useful in understanding contemporary treatments and historic trends in the treatment of resectable NSCLC.
- Additional real-world studies will be needed to fill the gaps in our understanding of the relative use of neoadjuvant, adjuvant and peri-operative therapy, as well as the chemotherapy regimens used, in resectable NSCLC.

Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/suppl/10.2217/fon-2021-1417

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