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Review article

Therapeutic modalities for superior sulcus tumor (Pancoast) tumor – A systematic review

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ABSTRACT

Background: Superior sulcus tumors (SST) are usually treated with multimodal therapy, mainly trimodal therapy encompassing radiochemotherapy (CRT) followed by surgery. However, high-level evidence from randomized trials remains limited. We conducted a systematic review to assess the evidence of treatment strategies considering adverse events and oncologic outcomes.

Methods: We systematically searched MEDLINE, CINAHL, EMBASE, Web of Science, CENTRAL, grey literature databases, and clinical trial registries. We included prospective and retrospective studies published between 1990 and 2024 with mono-, bi- or trimodal treatment reporting outcomes such as overall survival (OS), progression-free survival (PFS), resection rates, postoperative mortality/morbidity, and adverse events. Studies required histologically confirmed SST and a minimum of 30 patients.

Results: Thirty-five studies were included (28 retrospective, 7 prospective), with follow-up ranging from 10 to 107 months. Most studies originated from Europe (n = 16) and North America (n = 14). Sample sizes ranged from 30 to 2910 patients, predominantly male and aged in the late 50s to early 60s. Induction CRT protocols varied widely. R0 resection rates were reported in 33 studies, and trimodal therapy outcomes in 12. Hematotoxicity and esophagitis were the most common adverse events. Five-year OS rates varied between 11.8 % and 77 %, with trimodal therapy associated with better survival and distant metastasis as the dominant recurrence pattern. There were no studies addressing immunotherapy.

Conclusion: While trimodal therapy remains the guideline-endorsed standard for SST, comparative evidence remains sparse. The role of immunotherapy in induction regimens warrants further investigation.

1. Introduction

Superior sulcus (Pancoast) tumor (SST) is considered a special case of non-small cell lung cancer (NSCLC) that involves the lung apex and often adjacent vital structures, including the brachial plexus, subclavian vessels, and spine [1] causing a condition named the Pancoast-Tobias syndrome [2]. It is a rare, thoracic malignant disease [3] accounting for less than 5 % of all lung carcinomas [4]. The average age for Pancoast tumor occurrence is in the sixth decade of life and it is more common in men than in women [5]. Despite advances in treatment of lung cancer, the generalizability of treatment strategies to the subtype of SST remains an important issue that requires detailed consideration.

The prognosis for patients with this tumor subtype was poor in the past, but recent advances in treatment options showed marked improvement in survival rates [2]. A large study found that survival increased from 16 months to 22 months during the last decade.

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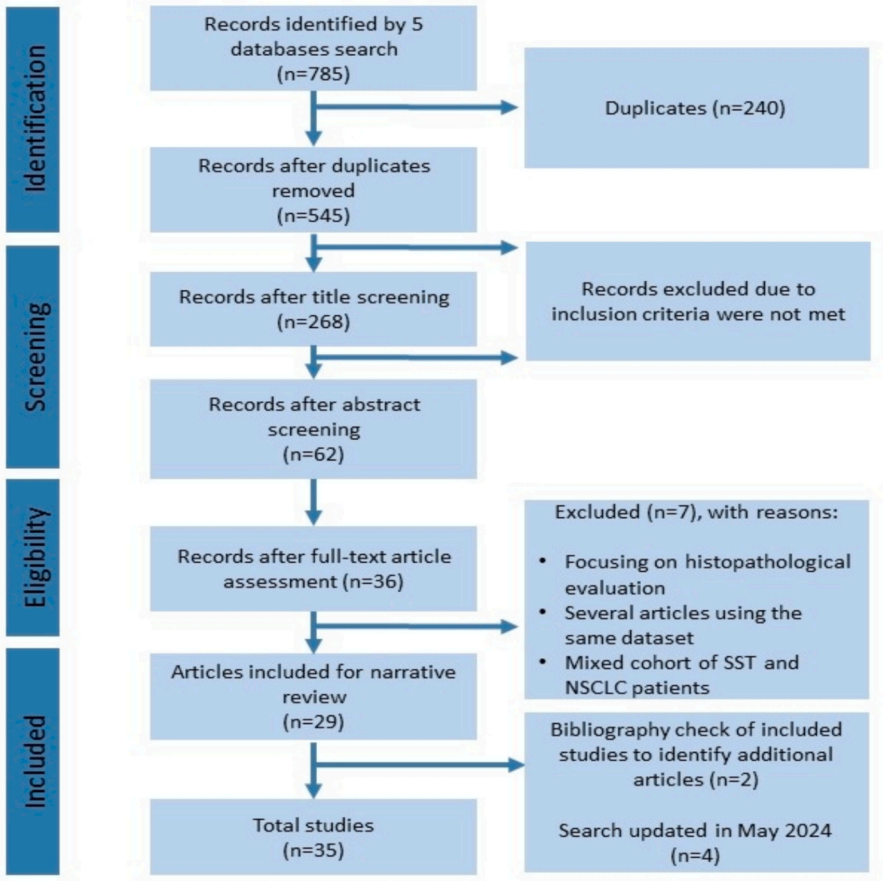

Fig. 1. Flow-chart of study selection process.

Prospective studies exploring treatment modalities have been scarce, due to the rarity of the tumor. In the last 30 years, guidelines for the treatment of the SSTs have incorporated the trimodality regimen, consisting of preoperative external beam radiotherapy, neoadjuvant chemotherapy and surgical resection. A prospective single-arm phase-II trial with long-term results published in 2007 showed that after neoadjuvant chemoradiotherapy followed by tumor resection, resection status is a relevant prognostic factor [6]. It is now considered to be the most effective treatment approach for SSTs and is recommended as the standard of care by the National Comprehensive Cancer Network (NCCN). On the other hand, the UK NICE Guideline [7] has recommended since 2011 to treat SSTs in the same way as other types of NSCLC and to offer multimodality therapy according to resectability, stage of the tumour and performance status of the person [7]. Thus, significant variability between available treatment options and even major discrepancies between international guidelines exist for this particular patient population. The published reviews on this topic did not directly address modern treatment concepts, considered only specific aspects [8] or their methodological approach was not comprehensive [9]. Our aim was to systematically search for all available evidence in the last three decades on treatment of SSTs and extract outcome data for different treatment concepts, including survival estimates, R0/1 resection rates, postoperative mortality and morbidity, in addition to the frequency and severity of adverse events post chemoradiotherapy.

2. Methods

This review was conducted according to the preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10].

2.1. Search strategy

A comprehensive literature search was conducted in August 2022 and updated in May 2024 using the following bibliographic databases: MEDLINE (PubMed), CINAHL, EMBASE, Web of Science, Central Cochrane Library (CENTRAL), including databases for grey literature and registries of clinical trials. The search strategy was developed using MeSH and keyword terms related to the main elements of the research question. The full search string is included in the Supplemental Materials Table 1. The study protocol was registered with the PROSPERO database (CRD42021282772).

2.2. Inclusion and exclusion criteria

Two independent reviewers (SL, LE) performed the title/abstract and the full-text screening according to the inclusion/exclusion criteria. Disagreements in the selection of articles were discussed with a third reviewer (DM). The reference list of all included articles was reviewed for potentially overlooked articles from the original literature search. Eligible studies were those that met the following inclusion criteria: (1) SST was confirmed by histology (pathological report); (2) Studies that reported on endpoints such as survival outcomes (overall survival (OS), disease-free survival (DFS), progression free survival (PFS). (3) The following study designs were taken into consideration: randomized controlled trials (RCTs), non-randomized clinical trials, observational comparative studies (cohort studies), retrospective case series with at least 30 participants, published in English or German, between 1990 and 2024; (4) If there were multiple articles published with the same dataset, the article reporting the largest sample size was selected for inclusion. The exclusion criteria were as follows: (1) Studies that did not report treatment modalities for SST and/or the focus was on different aspects,

Table 1
Characteristics of included studies.

First author	Year	Country	Sample size	Inclusion period for patients	Stage	Median FU (months)	Study design	Sex (m/w in %), Median/Mean age
Bolton, W D et al [12]	2009	USA	39 pat	1990–2006	Not reported	18 month	retrospective	74 %/26 % 56 years
Collaud, S et al [13]	2013	France	48 pat	1991–2012	Stage IIB, IIIA, IIIB	26 months	retrospective	65 %/35 % 62 years
De Leyn, P et al [14]	2009	Belgium	32 pat	2002–2008	Not reported	26.5 months	prospective	75 %/25 % 59.5 years
Demir, A et al [15]	2009	Turkey	65 pat	1994–2007	Not reported	28 months	retrospective	All patients were men 51.5 years
Favaretto, A et al [16]	2010	Italy	38 pat	1994–2008	IIB, IIIA, IIIB	Not reported	prospective	87 %/13 %61 years
Fischer, S et al [17]	2008	Canada	44 pat	1996–2007	Stage IIB, IIIA, IIIB	24 months	retrospective	62 %/38 % 61 years
Goldberg, M et al [18]	2005	USA	39 pat	1993–2000	IIB, IIIA, IIIB, IV	69 months	retrospective	64 %/36 % 59 years
Gomez, D et al [19]	2012	USA	32 pat	1994–2010	IIB, IIIA, IIIB, IV	53.4 months	prospective	63 %/37 %, age not reported
Hutchings, H et al [20]	2022	USA	2910 pat	2004–2017	Not reported	Not reported	retrospective	60.2 %/39.8 % 63.7 years
Ichiki, Y et al [21]	2012	Japan	50 pat	1992–2007	IIB, IIIA, IIIB, IV	Not reported	retrospective	90 %/10 % 61 years
Jeannin, G et al [22]	2015	France	36 pat	1992–2005	Not reported	38.6 months	retrospective	91 %/8 % 59 years
Kappers, I et al [23]	2011	Netherlands	115 pat	1994–2006	IIB, IIIA, IIIB	49 months	retrospective	69 %/31 % 56 years
Kernstine, K H et al [24]	2014	USA	46 pat	2003–2007	IIB, IIIA, IIIB	45 months	clinical trial	73 %/27 % 59 years
Kocak, Z et al [25]	2011	Turkey	33 pat	2001–2008	IIB, IIIA, IIIB, IV	17 months	retrospective	97 %/3 % 56 years
Kunitoh, H et al [26]	2008	Japan	75 pat	1999–2002	III, IV	68 months	prospective	88 %/12 % 57.5 years
Kwong, K F et al [27]	2004	USA	37 pat	1993–2003	IIB, IIIA, IIIB, IV	24.7 months	retrospective	59 %/41 % 55.5 years
Li, J et al [28]	2010	China	39 pat	1993–2005	IIB, IIIA, IIIB	RT group: 81 months RCh group: 45 months	retrospective	69 %/31 % RT: 56 yearsCRT: 52 years
Lin Tami, Y Y et al [29]	2021	Canada	32 pat	2000–2015	IB, IIB, IIIA	43 months	retrospective	44 %/56 % 59 years
Marra, A et al [30]	2007	Germany	31 pat	1993–2001	IIB, IIIA, IIIB	40 months	prospective	87 %/13 % 55 years
Marulli, G et al [31]	2015	Italy	56 pat	1994–2013	IIB, IIIA, IIIB	95 months	retrospective	84 %/16 % 64 years
McLaughlin, K et al [11]	2023	USA	155 pat	2000–2021	IIB, IIIA, IIIB	107 months	retrospective	52 %/48 % 58 years
Robinson, L A et al [32]	2018	USA	102 pat	1994–2016	IIB, IIIA, IIIB	72.5 months	retrospective	Not reported
Rusch, V W et al [33]	2006	USA	110 pat	1995–1999	not reported	82 months	clinical trial	69 %/31 % 56 years
Rzyman, W et al [34]	2023	Poland	47 pat	2007–2019	IIB, IIIA	65 months	retrospective	62 %/38 % 61 years
Shimada, Y et al [35]	2020	Japan	56 pat	2004–2016	IIB, IIIA, IIIB, IIIC	62.3 months	retrospective	93 %/7 % 64 years
Solli, P et al [36]	2017	Italy	94 pat	1998–2013	IIB, IIIA, IIIB	23 months	retrospective	84 %/16 % 62 years
Truntzer, P et al [37]	2014	France	42 pat	2000–2010	IIB, IIIA, IIIB	44.1 months	retrospective	74 %/26 % 54.7 years
Uchida, S et al [38]	2018	Japan	60 pat	1999–2017	Not reported	57 months	retrospective	94 %/6 % 53 years
Ünal, S et al [39]	2023	Netherlands	123 pat	2002–2017	IIB, IIIA, IIIB	59 months	retrospective	62.6 %/37.4 % 56.6 years
Vos, C G et al [40]	2014	Netherlands	30 pat	2002–2011	IIB, IIIA, IIIB	51 months	retrospective	57 %/43 % 53 years
Waseda, R et al [41]	2017	Austria	46 pat	1998–2013	IIB, IIIA, IIIB	42.3 months	retrospective	63 %/37 % 54.5 years
Weber, D J et al [42]	2014	USA	41 pat	1999–2012	Not reported	Not reported	retrospective	45 %/55 % 57.1 years
Wen, J et al [43]	2019	USA	384 pat	2004–2015	IIIA, IIIB	10 months	retrospective	59 %/40 % 66 years
Winkelman, J A et al [44]	2021	Netherlands	181 pat	2012–2019	IIB, IIIA, IIIB, IIIC, IV	Not reported	retrospective	63.5 %/36.5 % 60 years
Xue, Z et al [45]	2017	USA	81 pat	1997–2014	IIB, IIIA, IIIB, IV	22 months	retrospective	resected: 60 %/40 %, 61.5 years

[&]histologically confirmed, pat = patients, m/w = men/women, FU = follow-up, RT = radiotherapy, RCh = radiochemotherapy.

e.g. histopathological evaluation; (2) Conference abstracts, reviews, letters to the editor, case studies; (3) Articles describing treatment modalities for patients before the year 1990. The flowchart for study selection is shown in Fig. 1.

2.3. Data extraction

Data were extracted independently from all included studies by two authors (SL, LE) using a previously prepared and standardized template in Microsoft Excel. Potential discrepancies were discussed and clarified with a third reviewer (DM). The following information was extracted: (1) Publication data including author, year of publication, country; (2) Study design, number of patients, follow-up period; (3) Chemotherapy regimen, radiotherapy regimen, and surgical approach; (4) Demographic data, age, sex; (5) Clinical and pathological characteristics, including stage, completeness of resection (R0 and/or R1); (6) Survival data, including OS; (7) Local and distant recurrences; (8) Postoperative mortality; (9) Complications from chemoradiotherapy regimens.

2.4. Quality assessment

All selected articles were critically appraised using the Newcastle-Ottawa Scale for assessing the quality of nonrandomized studies. The risk of bias assessment tool by the Cochrane collaboration for randomized control trials (RCTs) or quasi-experimental studies [16] was used. Each cross-sectional study was rated low when it scored between 0–3, moderate for having a score of 4–6, and high with a score 7–8. Using the Cochrane collaboration tool, we assessed studies as low, unclear, or high risk of bias. Two reviewers (SL, LE) performed the assessment independently and disagreements were discussed afterwards (Table 3 and 4 in supplemental material).

2.5. Statistical analysis

Due to the substantial patient heterogeneity of included studies, a descriptive approach to presenting the results of the systematic review was chosen. Use of distinct therapeutic modalities and reported long-term outcomes were summarized in a descriptive thematic unit.

3. Results

3.1. Study characteristics

From a total of 785 hits, 35 articles on patients with SST between 1990 and 2024 were included in this review (Fig. 1). Twenty-eight studies were retrospective, while 7 were prospective studies, with reported follow-ups ranging from 10 to the longest follow-up of 107 months, as reported by McLaughlin, K et al. 2023[11]. Most of the studies were performed in Europe (16 studies) and North America (14 studies), with only 5 studies from Asian countries, predominantly from Japan (4 studies). Studies' sample size ranged from 30 to 2910 included patients. The patient population was predominantly men (60–90 % of patients), with a median age between 51.5 and 66 years. Most studies included patients with stage IIB, IIIA, IIIB and IV. Details about the included studies are reported in Table 1.

Twenty-six studies were rated as having high quality, and seven studies were rated as being of medium quality. The two prospective trials were rated as having an overall unclear risk of bias. The quality assessment of the articles is provided in the Supplemental material (Tables 3 and 4).

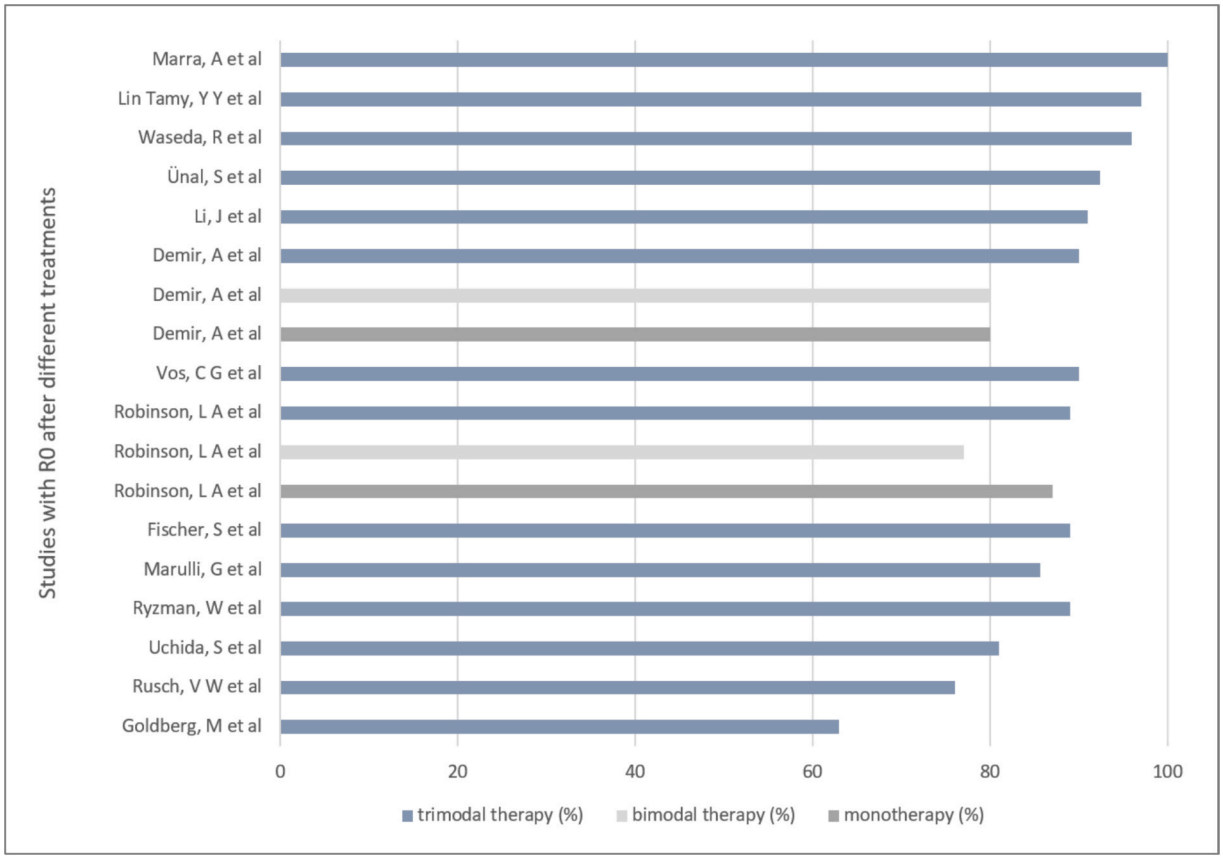

Fig. 2. Studies with R0 resection rate after trimodal therapy.

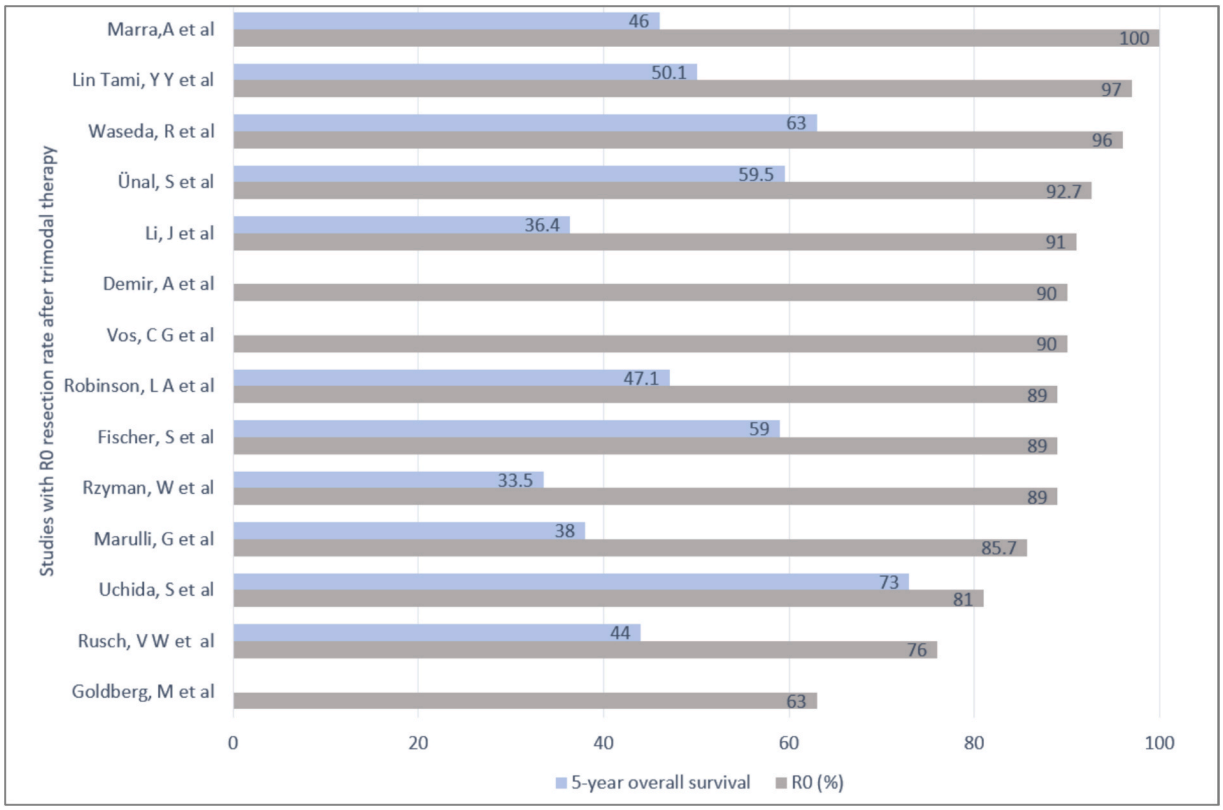

Fig. 3. Five-year survival for the entire patient cohort with trimodal therapy.

3.2. Resection rates and survival

Ten of 35 studies analyzed only trimodal therapy. Thirty-three of the 35 studies reported R0 resection rates, although 27 of 35 only referred to the entire sample not considering subgroup analyses by treatment modality. Fourteen studies reported R0 resection rates related to trimodal therapy (Fig. 2). Two of fourteen studies also considered R0 with other approaches (Fig. 2). Trimodality approach achieved good R0 resection rates varying between 63 % in Goldberg, M et al 2005 and 100 % in Marra et al. 2007 and Kappers,I et al 2011.

Five-year survival ranged from 11.8 % in Li et al. 2010 to 77 % in De Leyn, P et al. 2009 across all therapy modalities. In studies considering the trimodal approach 5-year survival varied between 33,5% in Rzyman et al. 2015 and 73 % in Uchida et al. 2018 in patients with complete resection (Fig. 3). Short-term mortality expressed as the 30-days mortality was generally low with a maximum of seven percent across all studies. Trimodal approaches achieved comparable results with a maximum of 6.9 % in Marra et al. 2007 (Table 2). Fig. 3 shows the 5-year overall survival reported by studies that used the trimodal treatment approach.

3.3. Radiotherapy treatment

3D-conformal thoracic radiation with a linear accelerator was the most frequently used radiotherapy modality with a dose between 30–66 Gy within a period of three to six weeks. Doses above 60 Gy were generally reserved for inoperable cases.

3.4. Chemotherapy treatment

The most frequently used regimen was induction, neoadjuvant chemotherapy with cisplatin or carboplatin for 2–3 cycles, with/or without etoposide. Chemotherapy regimens varied between studies, predominantly patients received carboplatin combined with mitomycin-C, vinblastine or vinorelbine (more frequently used in more recent studies). After surgery, as adjuvant treatment docetaxel was popular. In one study patients received three courses of cisplatin and etoposide. The most common side effects of radiochemotherapy were hematotoxicity, dysphagia and/or esophagitis and to a lesser extend infection and fatigue (Table 3).

3.5. Surgical treatment

The choice of the surgical approach was dictated on the basis of the location and local invasiveness of the primary tumor. The most frequently performed surgery was lobectomy with chest wall resection and in rarer cases segmentectomy, wedge resection, pneumonectomy and a chest wall resection alone (Table 4). Most common post-surgical complications were pneumonia (including ARDS and empyema), arrythmia and nerve injury (Table 3).

4. Discussion

To our knowledge this is the first systematic review on the multimodal management of SST. The only other published systematic review on this disease addressed the smaller subgroup of SST patients with spine involvement [8]. Other relevant reviews on the impact of multimodal therapy, in particular that of induction chemoradiotherapy, used non-systematic methods [9].

Our systematic search identified 35 studies, only seven of them were prospective and none were randomized. Therefore, direct comparisons between different treatment approaches, especially between trimodal concepts of neoadjuvant/induction radiochemotherapy followed by surgery and other non-trimodal concepts are difficult to make. Trimodal therapy was the approach that was most often pursued in the included studies. However, only few studies reported treatment results for different concepts separately. In consequence the results of patient groups with mixed treatment concepts might be considerably

Table 2
Results for treatment of SST in patient subgroups with **clearly distinguishable treatment concept** and outcomes (Chemotherapy, radiotherapy, radiochemotherapy with surgery, chemoradiation). Outcomes are presented for the subgroups with specified treatment concepts.

First author/ Year	Treatment modalities	n	R0 resection (%)	R1 resection (%)	Local/distant recurrence/ patients	30-day mortality	Overall survival	Comment
Bolton, W D et al. 2009	Tri_RCh_surg RT/ChT and surg Surgery with only adjuvant RT/ChT	12 4 23	22 (56)	17 (44)	Local: 11 Distant: 11 Local and distant: 1	Not reported	47 % (2-years), 27 % (5-years)	In total, 24 patients (62 %) received adjuvant treatment. In 4 patients the surgery was performed with palliative intention
Collaud, S et al. 2013	Tri_RCh_surg Bi_Ch_surg Bi_RT_surg M_surg	45 1 1 1	42 (88)	6 (12)	Local: 6 Distant: 8	6 % (3/ 48)	69 % (3-years), 61 % (5-years)	Only patients without evidence of distant metastasis that later underwent surgical resection
De Leyn, P et al. 2009	Tri_RCh_surg Bi_RCh Did not initiate therapy	27 3 2	25 (78)	2 (22)	Local: 2 Distant: 2	Not reported	74 % (5-years) Completely resected patients 77 % (5-years)	This article combined superior sulcus (cT3-T4) and central cT4 tumors
Demir, A et al. 2009	Tri_RCh_surg Bi_RT_surg M_surg	10 25 30	9 (90) 20 (80) 24 (80)	12 (18.5)	Not reported	6.2 % (4/ 65)	80 % (2-years) 59 % (2-years), 39 % (5-years) 59 % (2-years), 37 % (5-years)	Only included patients without mediastinal lymph node metastasis
Favaretto, A et al. 2010	Tri_RCh_surg Bi_RT_surg	37 1	28 (74)	10 (26)	Local: 6 Distant: 12	5.8 % (2/ 38)	40 % (5-years)	None
Fischer, S et al. 2008	Tri_RCh_surg	44	39 (89)	5 (11)	Local: 4 Distant: 9	0 % (0/ 44)	59 % (5-years)	The study focused on patients with SST where there was invasion of the thoracic inlet and by the resection of at least the first rib
Goldberg, M et al. 2005	Tri_RCh_surg Radiotherapy only, with possibly surgery No induction therapy, with possibly surgery	27 4 8	17/27 (63) Not reported Not reported	6/27 (22) Not reported Not reported	Local: 4 Distant: 8	5 % (2/ 39)	47.9 % (5-years)	Two patients were unresectable at thoracotomy after induction therapy, the number of patients that did not receive surgery with the other treatment modalities is unclear
Gomez, D et al. 2012	Tri_surg_RCh Bi_surg_RT_only M_surg	25 6 1	23 (72)	9 (28)	Local: 4 Distant: 14	0 %	72 % (2-years) 50 % (5-years) 45 % (10-years)	Patients received surgical resection first, followed by concurrent chemoradiation
Hutchings, H et al. 2022	Tri_RCh_surg Surg and adjuvant therapy	717 2193	Not reported	Not reported	Not reported	3.0 % (88/ 2910)	Not reported	Patients who received chemotherapy only or radiation treatment only before surgery were excluded from the analysis.
Ichiki, Y et al. 2012	Bi_R_surg M_surg	17 33	42/50 (84)	8/50 (16)	Described only for the R1 resection patients: Local: 4 Distant: 1	0 % (0/ 50)	32.7 % (5-years)	Analyses of only patients that underwent surgical treatment Ten patients received adjuvant chemo or radiotherapy postoperatively
Jeannin, G et al. 2015	Tri_RCh_surg Bi_RCh Incomplete Bi_RCh	16 18 2	15/16 (93.8)	1/16 (6.2)	Local: 7 Distant: 19	Not reported	57 % (5-years) for patients with resected disease 45 % (1-year), 16.9 % (2-years) for patients with unresectable disease	For the 18 patients with non-operable disease after the induction CRT, treatment was completed with boost RT of 22 Gy in 11 fractions and concomitant third cycle of Ch. Patients with N2-N3 were included
Kappers, I et al. 2011	Tri_RCh_surg Bi_RCh	19 30	19 (100)	0 (0)	Local: not reported Distant: 9	0 % (0/ 19)	74 % (2-years), 33 % (5-years)	None
Kernstine, K H et al. 2014	Tri_RCh_surg Bi_RCh	29 15	28 (97)	1 (3)	Local: 3 Distant: 10	7 % (2/ 29)	61 % (3-years)	None
Kocak, Z et al. 2011	Tri_RCh_surg M_surg Bi_RCh Inoperable, but received either radio, chemo or both	5 6 9 13	10/11 (91)	1/11 (9)	Local: 8 Both local and distant: 3 Distant: 9	Not reported	Curatively treated patients 2-years OS was 55 % Without surgery the 2-years OS was 41 % Palliatively treated patients 2-years OS was 18 %	Reported the entire patient population and not only selected cases
Kunitoh, H et al. 2008	Tri_RCh_surg Bi_RCh None	57 14 4	51 (89.5)	3 (5.3)	Local: 10 Local and distant: 9 Distant: 20	2.6 % (2/ 75)	61 % (3 years), 56 % (5 years)	None

(*continued on next page*)

Table 2 (*continued*)

First author/ Year	Treatment modalities	n	R0 resection (%)	R1 resection (%)	Local/distant recurrence/ patients	30-day mortality	Overall survival	Comment
Kwong, K F et al. 2004	Tri_RCh_surg	36	36 (97.3)	1 (2.7)	Local: 5 Distant: 13	2.7 % (1/37)	59 % (2-years)	Tumors deemed resectable by means of surgical intervention alone were excluded from this study
	Bi_RT_surg	1						
Li, J et al. 2010	Bi_RT_only_surg (1993–1999)	17	11 (65)	6 (29)	Local: 10 Distant: 5 Local and distant: 1	0 % (0/39)	41.2 % (2-years), 11.8 % (5-years)	None
	Tri_RCh_surg (since 1999)	22	20 (91)	1 (5)	Local 3 Distant: 9 Local and distant: 1		77.3 % (2-years), 36.4 % (5-years)	
Lin Tami, Y Y et al. 2011	Tri_RCh_surg	32	31 (97)	1 (3)	Local: 5 Local and distant: 1 Distant: 8	Not reported	67.9 % (2-years), 50.1 % (5-years), 31.8 % (10-years)	None
Marra, A et al. 2007	Tri_RCh_surg	31	29 (100)	0 (0)	Local: 1 Local and distant: 1 Distant: 7	6.9 % (2/29)	74 % (2-years), 46 % (5-years)	None
Marulli, G et al. 2015	Tri_RCh_surg	56	48 (85.7)	5 (8.9)	Local: 2 Distant: 22 Local and distant: 2	5.4 % (3/56)	38 % (5-years)	Patients with N2 disease were excluded
McLaughlin, K et al. 2023	Tri_RCh_surg Bi_Ch_surg Bi_RT_surg Surgery with adjuvant therapy	127 10 1 17	137 (88.4)	18 (11.6)	Local: 13 (8.3 %) Distant or combination with local: 48 (31 %)	0 % (0/155)	42 % patients with cT3 (5-years), 43 % patients with cT4 (5-years)	There was a mixture of patients (most) who received neoadjuvant therapy, and those who received adjuvant therapy only
Robinson, L A et al. 2018	Tri_RCh_surg	53	47 (89)	5 (9)	Local: 6 Distant: 0 Local and distant: 4	2 % (1/53)	47.1 % (5-years)	possible selection bias: preoperative treatment by external oncologist, only surgical candidates referred to center
	Bi_Ch_only_surg	34	26 (77)	8 (24)	Local: 7 Distant: 5 Local and distant: 0	3 % (1/34)	46.7 (5-years)	None
	M_surg_only	15	13 (87)	2 (13)	Local: 2 Distant: 2 Local and distant: 2	0 %	35.5 % (5-years)	subgroup contains only patients who refused preoperative therapy; patients usually received adjuvant therapy
Rusch, V W et al. 2006	Tri_RCh_surg	110	83 (76)	Not reported	Local: 10 Distant: 19	2.3 % ** (2/88)	44 % (5-years)	Two cycles of planned postoperative boost chemotherapy delivered in 45 % (49/110)
Rzyman, W et al. 2023	Tri_RCh_surg	47	42 (89)	Not reported	Local: 6 Distant: 9	2.1 % (1/47)	72.9 (1-year) 43.6 (3-years) 33.5 (5-years)	None
Shimada, Y et al. 2020	Tri_RCh_surg Bi_RCh Bi_Ch_surg	18 24 1	22 (92)	1 (4)	Resected patients: Local: 1 Distant: 8 Local and distant: 3	0 %	Resected patients: 68.8 % (5-years)	None
	M_RT_only M_Ch_only M_surg_only	2 6 5			Unresected patients: Local: 6 Distant: 10 Local and distant: 1		Unresected patients: 29.1 % (5-years)	
Solli, P et al. 2017	M_surg Bi_surg_RT: Bi_surg_Ch: Tri_surg_ChR: Bi_Ch_surg: Bi_RT_surg: Tri_RCh_surg:	13 29 1 3 38 1 9	85 (90.4)	8 (8.5)	Not reported	5.3 % (5/94)	51 % (2-years), 35 % (5-years), 23 % (10-years)	33 patients received postoperative treatments, most of them achieved a R0 resection (30/33)
Truntzer, P et al. 2014	Tri_RCh_surg	26	19 (86.4)	3 (13.6)	Local: 11 Loco-regional: 2 Distant: 15	Not reported	Patients with surgery: 63.6 % (1-year), 54.2 % (2-years), 37.5 % (5-years)	Number of patients treated with certain treatment modality differs between those reported in the tables and in the text
	Bi_RT_surg Bi_RCh_only	3 10					Patients with only R/Ch or just RT: 60 % (1-year),	

(*continued on next page*)

Table 2 (*continued*)

First author/ Year	Treatment modalities	n	R0 resection (%)	R1 resection (%)	Local/distant recurrence/ patients	30-day mortality	Overall survival	Comment
	M_RT_only	3					35 % (2-years), 25 % (5-years)	
Uchida, S et al. 2018	Tri_RCh_surg	54	44 (81)	10 (19)	Loco-regional: 3 Distant: 16	0 % (0/ 46)	Patients with complete resection 73 % (5-years) Patients with incomplete resection 51 % (5-years)	Patients with clinical N2 (mediastinal nodal metastasis) disease were excluded from the analysis
Ünal, S et al. 2023	Tri_RCh_surg	123	114 (92.7)	9 (7.3)	Local: 6 Distant: 35 Local and distant: 11	Not reported	72.4 (2- years) 59.5 (5-years) 48.1 (10-years)	None
Vos, C G et al. 2014	Tri_RCh_surg	30	27 (90)	3 (10)	Local: 3 Distant: 6	Not reported	60.7 % (2-years)	None
Waseda, R et al. 2017	Tri_RCh_surg	46	44 (96)	2 (4)	Local: 5 Distant: 12 Local and distant: 3	0 %	79 % (2-years) 70 % (3-years) 63 % (5-years)	Patients with disease progression were excluded from the study
Weber, D J et al. 2014	Tri_RCh_surg	34	37 (90.3)	4 (9.7)	Local: 5 Distant: 11	0 %	Cut-in patch-out group 48 % (5-years)	Only patients with removal of en-bloc at least 3 ribs were included.
	Bi_RT_only_surg	4					Posterolateral thoracotomy 12.5 % (5-year)	
	M_surg_only	3						
Wen, J et al. 2019	No treatment	106	Not reported	Not reported	Not reported	Not reported	49.4 % (1-year), 21.3 % (3-years), 15.8 % (5-years)	Study only included SST patients with T4 stage
	M_surg	21						
	M_RT	231						
	Bi_RT_surg	15						
	Bi_surg_RT	11						
Winkelman, J A et al. 2021	Tri_RCh_Surg	161	154 (85.1)	13 (7.2)	Not reported	3.3 % (6/ 181)	Not reported	None
	Bi_RT_only_surg	3						
	Bi_Ch_only_surg	7						
	Bi_immuno_only_surg	1						
	M_surg_only	8						
Xue, Z et al. 2017	Tri_RCh_surg	40	40 (83.3)	5 (10.4)	Not reported	4.2 % (2/ 48)	The 5-years OS for surgical patients was 54 % The 5-years OS for non-surgical patients was 20 %	Patients with M1 disease were excluded
	Bi_Ch_surg	2						
	Bi_RT_surg	2						
	Only_surg	4						
	No surgical intervention	33						

([§] estimated from graph, * In the example of Rusch, 2007, the authors calculate a percentage of patients resected divided by patients eligible for surgery. For the purpose of this review I would suggest to calculate a percentage of patients resected divided by patients entering the treatment concept (n = 110 in this case).
** percentage is for "postoperative mortality" (time period, e. g. 30 days not indicated).
RCh = Radiochemotherapy, ChR = chemoradiation, Ch= Chemotherapy, RT = Radiotherapy, surg= Surgery, C/R or R/C= Chemotherapy or Radiotherapy.
M = monomodal, Bi = bimodal, Tri = trimodal.

confounded. In detail, most studies reported more favorable oncologic outcomes such as higher R0 resection rates, however estimates differ remarkably between the considered trials [15,32].

The results of trimodal therapy with R0 resection rates varied between 63 % and 100 % and 5-year overall survival between 36 % and 63 % are satisfactory for the era before the introduction of immunotherapy. A question that needs to be answered from a clinical point of view is the time from the end of chemoradiation to surgery. Few included studies addressed this issue while we know from other disease entities such as esophageal cancer [46] that time to operation has an effect on survival. In addition, the question of radiotherapy volume and dose differed between studies. The most frequently used scheme varied between 45 and 50 Gy combined with platinum-based chemotherapy. Likewise, the role of hyperfractionation as proposed by some authors [47] is under debate. According to our data only few studies pursued such an approach making it difficult to evaluate hyperfractionation in the context of SST with high R0 resection rate and survival rates [30]. One important predictor is the realization of complete resections. Thus, the evaluation of resectability is key in the treatment process which is especially true for tumors with vertebral [12] or nodal involvement.

In order to achieve a favourable oncological outcome some authors suggested to alter the concept with preoperative chemotherapy and adjuvant radiation (Robinson 2018). In the light of advancing role of immunotherapy such adaptive approaches become even more attractive. Here, the Checkmate 816 trial found better event-free survival when Nivoloumab was added to neoadjuvant chemotherapy [48].

In clinical guidelines the preoperative trimodal approach is most often considered the standard of care for operable cases of SSTs. The NCCN guidelines already recommend for NSCLC (not specifically for SST) the addition of azetolizumab or pembrolizumab, or if applicable osimertinib in adjuvant setting after preoperative chemotherapy if PD-L1 levels are above 1 % (NCCN, MS-65). Nivolumab is mentioned by the NSSC guidelines as addition to chemotherapy solely for preoperative treatment [NCCN NSCL-E 2/6] according to the above-mentioned study. Likewise, for EGFR-positive patients, osimertinib (NCCN, MS-69/70) should be added to the trimodal treatment in the postoperative phase. Still preoperative chemoradiation is the standard of care for all patients.

It will be difficult to perform trials evaluating trimodal therapy plus addition of immunotherapy specifically in trials including only patients with SSTs. One such trial, JCOG 1807C (DEEP OCEAN) has been initiated by the Japan Clinical Oncology Group (JCOG) [Aokage, Jpn J Clin Oncol 2022]. In this prospective phase-II trial, patients with SST receive

Table 3
Results of treatment of pancoast tumor and complications.

First author/ Year	Type of surgery	Post-op complications In patients	Type of radiotherapy	Type of chemotherapy	Post-chemo(radio)-complications
Bolton, W D et al. 2009	Lobectomy: 26 Pneumonectomy: 2 Wedge resection: 11	Major complications: 11 Pneumonia: 8 Respiratory failure: 5 Pneumonitis: 1 Aspiration: 1 Empyema: 1	Preoperative radiation median dose: 46 Gy (range 6–64 Gy) Postoperative radiation median dose: 60 Gy (range 30–65 Gy)	Preoperative regimen Cisplatnin/VP-16: 3 Cisplatnin/vinblastine: 2 Cisplatnin/vinorelbine: 1 Carboplatnin/gemcitabine: 1Carboplatnin/taxol: 7	not reported
Collaud, S et al. 2013	Lobectomy: 46/48, Wedge resection: 2/48	Complications occurred in 10 pat: Dislocation of spinal instrumentation: 2 Cerebrospinal fluid leak: 2 Chylothorax: 1 Pulmopexy for left main bronchus kinking: 1 Thyroplasty for laryngeal nerve palsy: 1 Bowel resection for ischemia: 1 Completion pneumonectomy for bronchoarterial fistula: 1 Debridement for wound breakdown: 1	A total dose of 45 Gy in 35 patients	Two cycles of cisplatin-etoposide	not reported
De Leyn, P et al. 2009	Pneumonectomy: 11 Lobectomy/ bilobectomy: 16 Chest wall resection: 14	Atrial arrhythmia: 4, Pneumonia: 3 Sputum impaction: 2, Intense pain: 3,Prolonged air leak > 7 d: 1, Ileus: 1	45 Gy in fractions of 1.8 Gy in 5 weeks	Cisplatin (60 mg/m^2) – Etoposide (120 mg/m^2) in a 3 week schedule	Pneumonia: 1 Neutropenia: 5 Radiation oesophagitis: 2
Demir, A et al. 2009	Surgery was scheduled at 3–5 weeks after induction treatment. **Surgical procedure** wedge: 11/65lobectomy: 54/65	Overall complications: 17: Chylothorax: 3, Atelectasis: 2, Pneumonia: 2, Cerebrospinal fluid leakage: 1, Contralateral pneumothorax: 2, Prolonged air leak: 2, Hemorrhage requiring re-thoraco-tomy: 1, Wound infection: 1	The preoperative RT dose was 30–45 Gy	not reported	not reported
Favaretto, A et al. 2010	Lobectomy: 30; segmentectomy:4; not operated:4; resection rate: 89 %	Post-operative complicationsoccurred in 10 (29 %) pat	MVC(43 %)/21 NC: 16 MVC: 30 Gy/10F: 7 44 Gy/22F: 9 2 pat of NC did not complete RT = early death	16 pat MVC (43 %)/21 NC From 1994 to 1999, carboplatin combined with mitomycin-C and vinblastine From 2000 to 2007 carboplatin was combined with vinorelbine	First cycle: Haematological toxicity: 13 (35 %), Mucositis: 2, Second cycle: 11 (30 %), Third cycle: 3/16, Nausea/ vomiting: 6, Esophagitis: 9, Constipation: 11, Infection: 4, Neurotoxicity: 2,Asthenia: 6, Phlebitis: 1
Fischer, S et al. 2008	Lobectomy: 40 (90 %), pneumonectomy: 2 (5 %), wedge resection: 2 (5 %)	Pneumonia/respiratory failure: 10/44, Atrial fibrillation: 6/44, Empyema: 2/44, Wound dehiscence: 2/ 44, Chylothorax: 2/44, pulmonary emboli: 1/44, seizure: 1/44	Total dose of 45 Gy administered in 1.8 Gy daily fractions during 5 weeks	Two cycles of cisplatin (50 mg/m^2) and etoposide (50 mg/m^2)	not reported
Goldberg, M et al. 2005	Biopsy only: 1 Wedge resection: 2 Wedge and chest wall: 8 Lobectomy: 1 Lobectomy and chest wall: 25 Pneumonectomy: 1Pneumonectomy and chest wall: 1	Complications occurred in 31 % (12/34) patients Arrhythmia: 7 ARDS: 3 Phrenic nerve injury: 1 Bronchopleural fistula: 1	External beam RT delivered in daily fractions of 180 to 200 cGy for a total dose between 44 and 60 Gy	Regimen: cisplatin (50 mg/ m^2) and etoposide (50 mg/ m^2); or carboplatin (AUC2) and paclitaxel (50 mg/m^2); or carboplatin (AUC5) and paclitaxel (175 mg/m^2)	not reported
Gomez, D et al. 2012	Segmentectomy Lobectomy Pneumectomy (numbers not reported)	Pneumonia: 8/32 Pneumothorax: 6/32 Atrial fibrillation: 3/32 Urinary retention: 2/32	14 and 42 days after surgery. Depended on surgical outcome: negative margin: 60 Gy/ 50fractions/5weeks or positive margin: 64.8 Gy/54fractions	During RT, patients were given 2 cycles of oral etoposide at 50 mg/m2 daily on days 1 to 5 and 8 to 12 and bolus intravenous cisplatin at 50 mg/m2 on day 1. Depends on body surface area. After RCh and PCI had been completed, 3 more cycles cisplatin and	Dysphagia: 10/32 Pneumonitis: 1/32 Lung fibrosis: 1/32 Leukopenia: 2/32 Granulocytopenia: 3/32

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Table 3 (*continued*)

First author/ Year	Type of surgery	Post-op complications In patients	Type of radiotherapy	Type of chemotherapy	Post-chemo(radio)-complications
				oral etoposide, 1 cycle every 4 weeks.	
Hutchings, H et al. 2022	not reported	not reported	not reported	not reported	not reported
Ichiki, Y et al. 2013	Posterior approach: 47 Anterior approach: 3 (hemi-clamshell incisions) Segmentectomy: 2 Lobectomy: 50 Pneumonectomy: 1	Horner syndrome: 4 Paresthesia: 3 Arrhythmia: 2 Chylothorax: 1 Recurrent nerve palsy: 1 Dyshidrosis: 1	Preoperative radiotherapy not reported Postoperative radiotherapy 60 Gy	not reported	not reported
Jeannin, G et al. 2015	Lobectomy and atypic resection: 1 Lobectomy: 1 Bi-lobectomy: 10 Pneumonectomy: 4	Empyema: 2 Pneumonitis: 1 Prolonged atelectasis: 1 Pleural effusion: 1 OAP ACFA: 2 Cerebrospinal fluid break: 1	Three-dimensional (3D) conformal thoracic radiation was started on day 1 of CT with a linear accelerator. Mean dose of 44–45 Gy with daily 1.8 to 2 Gy in 22 or 25 fractions over 6 weeks.	Two courses of cisplatin (20 mg/m^2) − vinorelbine (20 mg/m^2) – 5-fluorouracil (5FU) (350 mg/m^2) with a 3-week interval. The second course of CT was started when the toxicities recovered to grade 1 or 0.	Febrile neutropenia: 1/36 Esophagitis: 25/36 Fatigue: 18/36 Renal failure: 1/36
Kappers, I et al. 2011	Surgery was scheduled 4–6 weeks after completion of CT a high-posterior or extended posterolateral approach was used Lobectomy:17 bilobectomy: 1segmental resection:1	Postoperative (acute) morbidity: 12/19 Severe acute morbidity: 9 (47 %); severe toxicity: 2 pneumonia: 5 subarachnoidal bleeding:1 chylothorax: 1 atelectasis: 1severe pain: 2	concurrent scheme of accelerated high-dose RT and daily low-dose CT The median dose of the induction CRT regimens in these 19 patients was 66 Gy	The preferred regimen was concurrent CRT(66 Gy + daily cisplatin 6 mg/m2).	Severe late toxicity of multimodality treatment: 3 Osteo-radionecrosis of the scapula requiring reconstructive surgery with a fasciocuta-neous flap 8 years after CRT and surgery (n = 1); dysfunction of the hand due to radiation-induced damage to the brachial plexus-6 years after ChR and surgery (n = 1); osteo-radionecrosis of theirradiated ribs (after 4 years) with a bronchopleural fistula causing empyema (after 8 years) followed by a spontaneous perforation ofthe thoracic wall 11 years after CRT and surgery (n = 1).
Kernstine, K H et al. 2014	upper lobectomy: 24 segmentectomy: 2 bilobectomy: 2wedge resection: 1	not reported	Initiated simultaneously with thoracic RT given daily Monday through Friday in 1.8-Gy fractions to a total dose of 45 Gy.	induction therapy with cisplatin-etoposide, concurrently with thoracic radiotherapy at 45 Gy. Consolidation consisted of docetaxel every 3 weeks for 3 doses. cisplatin (50 mg/ m2intravenously) on days 1, 8, 29, and 36, and etoposide (50 mg/m2 intravenously) days 1 through 5 and 29 through 33	Dehydration:2 Diarrhea:1 Dyspnea:2 Fatigue1 Nausea:1 Vomiting:1 Weight Loss:1 Hypoxia:1 Infection:1 w/neutropenia grade 3:1Neutropenia:3
Kocak, Z et al. 2011	Wedge and chest wall: 2 Lobectomy: 4 Lobectomy and chest wall: 5	Pleural effusion: 2 Shoulder instability: 1	Total dose 45–46.8 Gy in fractions of 1.8–2 Gy in 5 weeks for the operable patients For inoperable and metastatic patients radiation doses ranged between 30 to 65 Gy in fractions of 1.8–3 Gy	Two cycles (one patient three cycles) of cisplatinum (50 mg/m^2) and etoposide (50 mg/m^2); for one patient taxotere (75 mg/m^2)	not reported
Kunitoh, H et al. 2008	57 (76 %) underwent surgical resection (lobectomy: 53, probe thoracotomy: 1, other: 3)	ARDS: 2/75 Empyema: 2 Pneumonitis: 1 Chylothorax: 1	RT directed at the tumor and theipsilateral supraclavicular nodes was started on day 2 of each course (C), total dose of 45 Gy/25 fractions, with a 1-week split. First: 27 Gy/15 fractions/ 3weeks. Second: 18 Gy/10 fractions/2weeks	Patients received two cycles of Ch every 4 weeks as follows; mitomycin 8 mg/m2 days 1 and 8, and cisplatin 80 mg/m2 on day 1, vindesine 3 mg/m2 on day 1 and 8 (MPV)	Infection: 7/75 Anemia: 5/75 Fever: 2/75 Leucopenia: 63/75 Neutropenia: 62/75 Diarrhea: 1/75 Thrombocytopenia: 11/75

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Table 3 (*continued*)

First author/ Year	Type of surgery	Post-op complications In patients	Type of radiotherapy	Type of chemotherapy	Post-chemo(radio)-complications
Kwong, K F et al. 2005	Posterior-lateral, anterior–superior, and anterior hemiclamshellthoracotomies. Lobectomies: 34 Pneumonectomies: 3	ARDS: 2 Bronchopleural fistula: 2 DVT: 2 Prolonged atelectasis: 2 Pulmonary embolus: 1 Pneumonia: 1 Hand paresthesia: 1Pleural effusion: 1	Mean total radiation dose: 56.9 Gy. Three-dimensional conformal RT was administered as a large-field 45-Gy dose to the primary tumor and mediastinum, followed by a small-field boost to the primary tumor beginning at 14.2 Gy.	Weekly platinum-based combination chemotherapy was used in the majority of patients. Carboplatin and paclitaxel: 25; cisplatin and etoposide: 7; cisplatin and vinorelbine: 2	not reported
Li, J et al, 2010	Lobectomy: 11 Lobectomy plus chest wall: 17 Pneumonectomy: 6Pneumonectomy plus chest wall: 5	In the RT group: Atelectasis: 2, Pneumonia: 1, Bronchopleural fistula: 1 In the RCh group: Pneumonia: 2;Prolonged air leak: 1; Bronchopleural fistula: 1	Patients who received RT had a preoperative mean dose of 45 Gy (range, 36–60 Gy) delivered in daily 1.8–2 Gy fractions (5 days/week).Patients who received CT/RT had a pre-operative mean radiation dose of 45 Gy (range, 36–54 Gy) administered in daily 1.8 Gy fractions (5 days/ week).	Two cycles of cisplatin and etoposide with concurrent RT. Cisplatin 50 mg/m2 was administered on days 1, 8, 29, and 36. Etoposide 50 mg/m2 was administered on days 1–5 and 29–33	Leukopenia: 8 Neutropenia: 7 Thrombocytopenia: 5 Anemia: 3 Esophagitis: 1 Nausea: 3 Vomiting: 3Fatigue: 4
Lin Tami, Y Y et al. 2021	Lobectomy: 30Wedge resections: 2	Not reported	31 (97 %) patients underwent three-dimensional conformal RT, and 1 (3 %) intensity-modulated RT. 31 (97 %) completed full radiation dose of 45 Gy	Induction ChR included 2 cycles of cisplatin/ carboplatin-etoposide chemotherapy concurrently with RT	Not reported
Marra, A et al. 2007	Wedge resection: 3 Segmentectomies: 3 Lobectomies: 22 Pneumonectomy: 1	Two patients suffered a pleural empyema with bronchial fistula and another underwent re-thoracotomy due to post-operative bleeding.	Twice-daily hyperfractionated accelerated radiotherapy (1.5 Gy per fraction more than 6 h apart, 5 days per week, to a total dose of 45 Gy over a period of 3 weeks	Three courses of split-dose cisplatin 60 mg/m2 i.v. on days 1 and 7 and etoposide 150 mg/m2 i.v. on days 3,4, and 5 or paclitaxel (since 1999) 175 mg/m2 i.v. on day 1	Grade 3–4 toxicity was observed in 32 % of cases. Major complications arose in 20.6 % of the patients. Esophagitis: 5; Leukopenia: 4; Anaemia:4; Thrombocytopenia:4; Nausea:2; Vomiting:2; Thromboembolism:2; Stomatitis: 1
Marulli, G et al. 2015	Lobectomy: 42 (75 %) Segmentectomy: 13 (23.2 %) Wedge resection: 1 (1.8 %)	Haemothorax: 2; Empyema: 1; Paraparesis due to a bleeding inthe vertebral canal: 1; Bronchial stenosis requiring the positioning of a bronchial stent: 1; Wound dehiscence: 1;	From 1994 to 1996: 30 Gy; 3 Gy every fraction, five fractions per week (from Days 22 to 35) using a two-dimensional technique with opposed fields. From 1997 to 2013, patients were given a RT regimen 44 Gy in 2 Gy fractions, 5 fractions per week over 4.5 weeks (from Days 22 to 52) using a uniform conformal technique.	Induction therapy: 2–3 cycles of a platinum-based Ch with RT (30–44 Gy) 1994 to 1999: patients received carboplatin AUC 5 mg/ml/min on Days 1 and 22, combined with mitomicin-C 8 mg/m2 on Days 1 and 22 and vinblastine 4 mg/m2 on Days 1, 8, 22 and 29 (MVC). 2000 to 2013, carboplatin was combined with vinorelbine (Navelbine®) 25 mg/m2 on days 1, 8, 22 and 29 (NC).	not reported
McLaughlin, K 2023	Wedge/segment: 18 Lobectomy: 130 Bilobectomy: 3 Pneumonectomy: 4	Not reported	Radiation doses were classified as preoperative (44–55.8 Gy), definitive (57.59 Gy or greater), palliative (<44 Gy)	Most patients received a preoperative platinum containing chemotherapy regimen, carboplatin: 39 patients, cisplatin: 90 patients or other: 3 patients	not reported
Robinson, L et al. 2018	Lobectomy: 70 (69 %) Pneumonectomy: 1 (1 %)Segmentectomy: 27 (26 %)Wedge resection: 4 (4 %)	Atrial arrhythmias: 10; Air leak > 5 days: 34; Pneumonia: 8; Atelectasis requiring bronchoscopy: 14; ARDS: 8; DVT: 4; Chylothorax: 5	For the trimodal group: 45 Gy For the bimodality group: 66 Gy delivered 6 weeks postoperatively to the resection bed	For the trimodal group: 2 cycles of induction platinum-based doublet chemotherapy. For the bimodality group: 3 cycles of platinum-based doublet chemotherapy	not reported
Rusch, V W et al 2007	Lobectomy/pneumonectomy	Atelectasis: 13/88; pneumonia: 12/88; Atrial arrhythmia:10/88; Empyema: 5/88; Hemorrhage, reoperation: 2; Myocardial infarction: 2;	Radiation: 180 cGy daily X 5 weeks (45 Gy total)	Cisplatin: 50 mg/m2, days 1, 8, 29, 36 Etoposide: 50 mg/m2, days 1–5, 29-33Radiation: 180 cGy daily X 5 weeks (45 Gy total)	Leukopenia: 41 Neutropenia: 41 Anemia: 18 Esophagitis: 5 Nausea: 7 Vomiting: 8Fatigue: 10

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Table 3 (*continued*)

First author/ Year	Type of surgery	Post-op complications In patients	Type of radiotherapy	Type of chemotherapy	Post-chemo(radio)-complications
		Bronchopleural fistula: 2; Ventricular arrhythmia: 2; Wound Infection: 2;			
Rzyman, W et al. 2023	Segmentectomy: 2 Lobectomy: 45	Arrhythmia:10 Pneumonia: 5 Atelectasis: 2 Frequent aspiration: 2	45–66 Gy in 25 and 33 fractions	Cisplatin etoposide: 41 Cisplatin vinorelbine: 3 Carboplatin paclitaxel: 2 Cisplatin pemetrexet: 1	21 patients developed grade 3–4 side effects, such as neutropenia: 17 (35.4 %), sepsis: 1 patient, thrombocytopenia: 1 patient, pneumonia: 1 patient, acute renal failure: 1 patient
Shimada, Y et al. 2020	Lobectomy: 23 (96 %) Pneumonectomy: 1 (4 %)	Wound infection: 3 Prolonged air leak: 2 Horner syndrome: 2 Cerebrospinal fluid leakage: 2 Pneumonia: 1 Empyema: 1Others: 4	In the resected group 13 patients received 40–49 Gy, while 5 patients received 50–59 Gy. In the unresected group 3 patients received 40–49 Gy, 1 patient received 50–59 Gy, and 22 patients received $\geq$ 60 Gy	Resected patients received platinum-doublet chemotherapy, 2–4 cycles of CDDP-based or CBDCA-based treatment, while unresected patients received either CDDP-based or CBDCA-based treatment or, vinorelbine, docetaxel, tegafur-gimeracil-oteracil separately	Not reported
Solli, P et al. 2017	Lobectomy: 78 Pneumectomy: 3 Bronchial sleeve: 5 Wedge resections: 7	major complication: 15/94 reoperation: 6, ARDS: 5, hemothorax: 3, chylothorax: 2, neurological failure: 2, empyema: 1, pulmonary embolism: 1, severe pneumonia: 1	Received induction treatments up to 45 Gy	3 cycles of induction chemotherapy, specifics not reported	not reported
Truntzer, P et al. 2014	Lobectomy: 22/42 (50 %) En-bloc resection lobectomy Surgery: 22/42 (50 %) En-bloc resection: 2 (9.5 %) En-bloc resection + lymph node dissection: 20 (90.5 %)	Post-surgery complications: 13/22 (59 %) Neuropathic pain: 6 (27.3 %), respiratory distress: 3 (13.6 %),lung infection: 3 (13.6 %) brachial plexite: 2 haemoragia:1	Delivered with 3D conformal RT by linear accelerator for 38 pat (90.5 %) or by intensity modulated RT: 4 pat (9.5 %). In total 66 Gy (only one pat) or 46 Gy (most) Median delivered irradiation dose was 46 Gy (40–47 Gy). Preoperative and exclusive median radiotherapy doses were 46 Gy (40–47 Gy) and 51.8 Gy (40–70 Gy),	In total, 36 patients cisplatin-vinorelbine: 23 patients carboplatine-paclitaxel: 10 patientsunknown: 3 patients	hematoxicity: 13 patients febrile neutropenia: 6 patients nausea and/or vomiting: 7 patientshearing loss: 1 patient
Uchida, S et al. 2018	Surgery was performed 2–6 weeks after completion of induction therapyRight upper lobectomy: 36 (67 %) Left upper lobectomy: 17 (31 %) Left pneumonectomy: 1 (2 %)	Pneumonia: 2 (4 %) Chylothorax: 2 (4 %) Empyema and interstitial pneumonitis: 1 (2 %) Cerebral infarction and interstitial pneumonitis: 1 (2 %) Prolonged air leakage: 1 (2 %)	The total radiation dose: 45 Gy in 25 fractions.End of 2011 3D radiotherapy was used instead of 2D radiotherapy	From 1999 to 2008, 2 cycles of mitomycin–vindesine cisplatin (MVP) CT with a 4-week interval. Cisplatin at 80 mg/m2 and mitomycin at 8 mg/m2 were administered on ChT day 1, and vindesine was administered at 3 mg/m^2 on days 1 and 8. From 2009 to 2017, the 2 cycles of cisplatin at 80 mg/m^2 and vinorelbine at 20 mg/m^2 on day 1 and bolus vinorelbine at 20 mg/m^2 on day 8 (PV) during RT. 35 (65 %) pts MVP therapy, 19 (35 %) PV therapy	Leucopenia: 30 (56 %) Neutropenia:29 (54 %) Nausea: 1 (2 %) Vomiting: 1 (2 %) Lung infection:1 (2 %)
Ünal, S et al. 2023	Lobectomy/Lobectomy with chest wall resection: 113 Wedge resection/Wedge and chest wall: 6 Segmentectomy: 2 Other: 2	not reported	The preoperative radiotherapy dose was 39–66 Gy	not reported	not reported
Vos, C G et al. 2014	Upper lobectomy by (Shaw–Paulson) with en bloc resection of the involved chest wall	Not reported	The standard induction RT dose evolved over time from 39 Gy/13 fractions, to 46 or 50 Gy/	Induction CR typically consisted of three courses of platinum- based chemotherapy	not reported

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Table 3 (*continued*)

First author/ Year	Type of surgery	Post-op complications In patients	Type of radiotherapy	Type of chemotherapy	Post-chemo(radio)-complications
	and the T1 branch of the brachial plexus.		23 or 25 fractions. RT was commenced with the second cycle of Ch.		
Waseda, R et al. 2017	Lobectomy: 37 (80 %) Pneumonectomy: 6 (13 %) Sublobular resection: 3 (7 %)	Hemorrhage: 3, Wound infection: 2, Pneumonia: 2, Brachial plexopathy: 2, Empyema: 1, Chylothorax: 1	Median dose delivered was 53 Gy (range 45–66 Gy)	3 cycles of platin-based doublet chemotherapy. 43 patients underwent 2–4 cycles of cisplatin doublet therapy, 3 patients received 2–3 cycles of carboplatin doublet therapy. Additionally, vinorelbine: 18, etoposide: 13, gemicitabine: 8, docetaxel:7 patients	Leukopenia in (n = 14; 24 %), neutropenia (n = 12; 21 %), anemia (n = 1; 2 %), thrombocytopenia (n = 3; 5 %), esophagitis (n = 5; 9 %), nausea/emesis (n = 1; 2 %).
Weber, D J et al. 2014	Surgery was accomplished by either a "cut-in patch-out" technique (n = 25) or traditional posterolateral thoracotomy and separate chest wall resection (n = 16).	Wound infection: 2 Pneumonia: 7 Reintubation: 10 Tracheostomy: 7 Pulmonary embolism: 3Bronchopleural fistula: 2	Not reported	not reported	not reported
Wen, J et al. 2019	Lobectomy: 25 (53.2 %), Partial wedge resection: 16 (34.0 %), Pneumonectomy: 6 (12.8 %)	not reported	not reported	not reported	not reported
Winkelman, J A et al. 2021	VATS: 8 Thoracothomy: 159 Pneumonectomy: 1 Bilobectomy: 4 Lobectomy: 166 Segmentectomy: 4 Wedge resection: 6	Prolonged air leakage: 18 (9.9 %) Pneumonia: 40 (22.1 %) Other Infections: 23 Bleeding (+ reintervention): 8 Chylothorax: 6 Atelectasis: 18 (9.9 %) Recurrent nerve damage: 1 Phrenic nerve damage: 7 ARDS: 2 (1.1 %); Supra-ventricular arrhythmia: 10 (5.5 %) Myocardial infarction: 1 TIA/CVA: 1	guidelines recommended trimodal treatment (Not reported)	not reported	not reported
Xue, Z et al. 2017	Lobectomy: 39 patients Wedge resection or segmentectomy: 6 patients Bilobectomy: 2 patientsPneumonectomy: 1 patient	Respiratory failure: 12; Pneumonia: 10; Atrial fibrillation: 6; Atelectasis: 5; Pulmonary embolism: 4; Wound infection: 4 Hemothorax/bleeding: 4; Prolonged air leak: 3; Cardiac arrhythmia: 3; Venous thrombus: 3; Diarrhea: 3; Urinary tract infection: 2; Postoperative delirium: 2; Agitation: 2; Other:6	Radiation dose: 40—50 Gy: 26 >50 Gy: 9 Unknown: 7	Cisplatin and etoposide: 24 Taxol and carboplatin: 9Other or uncertain: 9	not reported

RCh = Radiochemotherapy, ChRTCT= Chemoradiotherapy, Chemotherapy, RT = Radiotherapy, S= Surgery, C/R or R/C= Chemotherapy or Radiotherapy, fr = fraction, Gy = grey, pat = patients, postop = postoperative.

Table 4
Type of surgery in 1503 cases.

Type of surgery	Frequency N = 1503
Lobectomy/Lobectomy with chest wall	**1261 (83.9 %)**
Wedge resection/Wedge and chest wall	**76 (5.1 %)**
Pneumectomy	**59 (3.9 %)**
Segmentectomy	**60 (4.0 %)**
Chest wall resection	**30 (2.0 %)**
other	**17 (1.1 %)**

preoperative chemoradiotherapy with 66 Gy and concomitant cisplatin and S-1, followed by two courses of durvalumab and are then evaluated for surgery, after which additional 22 courses of durvalumab are given. Unresectable patients without progression also receive 22 courses of durvalumab. However, this is a single-arm trial evaluating primarily efficacy and safety of the aforementioned treatment. Another study testing the addition of atezolizumab to chemoradiation in SST was withdrawn due to no accrual, underlining the difficulty in the treatment of SST (ClinicalTrials.gov ID NCT04989283).

The extension of the classical trimodal approach with modern immunotherapy and/or EGFR targeted treatment, e. g. quadramodal treatment of SSTs including immune checkpoint blockade, underlines the need to mitigate treatment related toxicities. In our review, neutropenia and dysphagia were the most common complications. However, surgery could be performed in the majority of patients which reveals that the toxicity profile of preoperative chemoradiation does not prevent surgery. The difficulty to perform randomized trials in this setting warrants the need to search for alternative sources of evidence such as retrospective data based on clinical registries. Another key question is how SST differ from any other type of NSCLC and how results from trials with broader inclusion criteria can be applied to SSTs.

As immunotherapy and osimertinib are already recommend in the NCCN guidelines the current questions are reduced to the neoadjuvant/perioperative role of immunotherapy in SST. Toxicities varied between studies occurring in about 30 % of the patients while they were

treatment limiting in the minority of cases. The question arises how immunotherapy when given preoperatively might alter rates of toxicity. Considering prospective data, when added to chemotherapy, immunotherapy increased adverse events only mildly [48]. In addition, the introduction of adjuvant treatment might change the predictive value of R0 resection. Here, we again need new observational data from the modern era.

5. Limitations

In the light of recent developments with immunotherapy as the standard of care for stage III NSCLC added to chemoradiotherapy, our results need careful interpretation. By the time of writing, we found no study evaluating the effect of immunotherapy as a further component in the multimodal treatment of NSCLC. When it comes to radiotherapy the advent of modern technologies such as PET-based planning demonstrated in the PET-plan study might alter the prevalence of side effects. This is also true for conformal techniques such as VMAT which allows for a more conformal treatment. Both methods were not ubiquitously available.

The studies considered in our review were very heterogeneous in nature with a wide range of approaches studied. This makes it especially challenging to identify a singular modality with the most benefit for lung cancer patients. In addition, most studies failed to report stratified analyses in terms of clinically important outcomes. The merger of treatment groups warrants the analyses of individual patient data which was out of the scope for this study. The retrospective nature of most trials hampers the clinical evidence thus a conclusive interpretation of their results. Because of the limited sample size, model adjustment is virtually impossible making confounding likely. In these light, larger trials with adequate sample sizes are needed allowing for modern statistical methods, such as emulating clinical trials.

As mentioned earlier new diagnostic tools such as PET might have shifted the staging towards higher oncological stages. The study limitations stem from the limitations of the included original studies. Most of the study results have been derived from a relatively small sample size of patients with SSTs. This could have biased patient's prognosis and the effectiveness of induction treatment and multimodal treatment. As most studies are retrospective in nature, there is a potential for selection bias. There could be biases arising from differing surgical techniques and perioperative care strategies by changes in medical care. This is due to SST being a relatively uncommon presentation of lung cancer. Many of the induction CRT schemes altered over time.

Especially the advent of immunotherapy might alter any conclusions drawn from previous trials. The evidence from prospective trials focusing on neoadjuvant/perioperative immunotherapy might likewise apply to SST. However, further trials are needed to address this multimodal therapy [49].

6. Conclusion

Despite the limited evidence, we found preoperative chemoradiation remains the standard in most guidelines. There are several issues that require further investigation, such as which candidates are amenable to resection, how does definitive therapy compare with surgical resection, and what are predictors of survival among surgical and nonsurgical patients.

CRediT authorship contribution statement

Susan Langer: Writing – original draft, Visualization, Formal analysis. **Daniel Medenwald:** Writing – original draft, Formal analysis, Conceptualization. **Dirk Vordermark:** Writing – review & editing, Conceptualization. **Wolfgang Schuette:** Writing – review & editing. **Karl-Matthias Deppermann:** Writing – review & editing. **Monika Nothacker:** Writing – review & editing, Conceptualization. **Stephan Eggeling:** Writing – review & editing. **Ljupcho Efremov:** Writing – original draft, Visualization, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.lungcan.2025.108640.

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