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REVIEW

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The role of surgery for anaplastic thyroid carcinoma in the era of targeted therapeutics: A scoping review

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Abstract

Background: Questions exist regarding patient selection for surgery in anaplastic thyroid carcinoma (ATC), particularly with the advent of neoadjuvant-targeted therapeutics. The present scoping review sought to evaluate what extent of surgical resection should be performed in ATC.

Methods: A scoping review was carried out in accordance with Joanna Briggs Institute and the preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR) protocols. Included studies were required to provide clear description of the surgery performed for ATC.

Results: The final search identified 6901 articles. Ultimately only 15 articles including 1484 patients met inclusion criteria. A total of 765 patients (51.5%) underwent attempted curative intent surgery. The approach to resection of adjacent tissues varied between studies. Eight studies considered laryngeal ± pharyngeal resection (8/15, 53.3%), eight studies (53.3%) considered tracheal resection and again eight studies (53.3%) considered esophageal resection. More extensive resections increased morbidity without improving overall survival (OS) (<9 months in the 12 studies using a combination of surgery and chemoradiotherapy). In the three studies utilizing targeted therapy in addition to surgery, OS was notably improved while surgical resection following neoadjuvant therapy was less extensive.

Conclusions: There is no clear agreement in the literature regarding the limits of surgical resection in locoregionally advanced ATC. A definition of surgically resectable disease will be required to guide surgical decision making in ATC, particularly with the potential to reduce tumor burden using neoadjuvant targeted treatment in suitable patients.

Level of evidence: III

KEYWORDS
anaplastic, surgery, targeted therapy, thyroid, unresectable

1 | INTRODUCTION

Anaplastic thyroid cancer (ATC) is a rare, aggressive form of thyroid cancer (<2% of cases) which disproportionately accounts for 20% to 50% of all thyroid cancer related deaths.[1,2] The median overall survival (OS) of patients diagnosed with ATC is 3 to 6 months.[3,4] At present multimodal therapy combining systemic treatment and ablative surgical resection offers the only potential for prolonged survival or cure.[5] Recent advancements in our understanding of the molecular pathogenesis of this disease has resulted in the innovation of new targeted therapeutic regimens such as *BRAF/MEK* inhibitors, offering hope of improved clinical outcomes.[6] Combined treatment with dabrafenib-tremetinib was approved by the FDA in 2018 for *BRAF V600E* somatic mutated tumors in anaplastic thyroid cancer. Further developments in targeted therapies for *RET*, *NTRK* and *ALK* mutated tumors may also add to available treatment options.

All patients with ATC are stage IV by definition irrespective of disease extent. Intrathyroidal disease is staged as IVA, extrathyroidal or locoregional disease is staged as IVB, while metastatic disease is staged as IVC.[7] According to the 2021 American Thyroid Association (ATA) guidelines for management of patients with ATC, those with stage IVA and 'resectable' stage IVB disease should be offered upfront surgical resection.[8] This is supported by a recent systematic review demonstrating the survival benefit of surgical resection in stage IVA and IVB disease with an R0/R1 resection.[9] The ATA guidelines do not strictly define the tumor or nodal features that would deem disease to be considered 'resectable' in ATC. Thus, the definition of 'resectable' disease may vary from surgeon to surgeon. This is of crucial importance as resecting critical adjacent structures in the neck such as the trachea, pharynx or larynx significantly increases post-operative morbidity.[10,11]

Given the dismal prognosis for the majority of patients with ATC, any surgical intervention must aim to preserve quality of life, in addition to extending length of life.[8] Thus, ablative procedures causing significant morbidity may not be in the patient's best interest. With recent evidence demonstrating responses to neoadjuvant targeted therapeutics in ATC, the treatment paradigm of extrathyroidal ATC is changing, offering the potential to dramatically reduce primary tumor extent prior to potential surgical intervention.[5,12] Thus, clear definitions of resectability will be paramount in order to ensure appropriate patient selection for potentially curative surgical resection.

The present scoping review seeks to explore what extent of ATC was considered 'resectable' by in the existing literature. In addition, it seeks to evaluate the OS of patients with ATC depending on both surgical and disease extent, the impact of neoadjuvant targeted therapy on the extent of resection and OS, the timing of surgery following neoadjuvant targeted therapy, and the post-operative morbidity of patients undergoing differing surgical resections for ATC.

2 | METHODS

This review was conducted in accordance with the Joanna Briggs Institute protocol for scoping reviews while reporting of data was performed in alignment with the preferred reporting items for systematic reviews and meta-analyses extension for scoping reviews (PRISMA-ScR) protocol.[13,14] The need for ethical approval was waived as this was a review article. This study was not preregistered as it was a scoping review ineligible for registration with PROSPERO.

2.1 | Search strategy

The search of the literature was performed using Pubmed/MEDLINE on the June 14, 2023. The following terms were used:

1. (anaplastic thyroid)
2. AND (surgery OR surgical OR resection OR resectability OR resected OR unresectable OR extirpation)

Manuscripts included in the scoping review had their references stored in EndNote 20 and manually screened for additional relevant studies and this search yielded 6901 studies.

2.2 | Eligibility criteria

Eligible studies reported on a population of patients with ATC with at least a subset of patients undergoing surgical resection. To be eligible for inclusion, studies needed to clearly delineate the extent of surgical resection performed or provide a definition of tumors they considered unresectable. Case reports, case series, randomized trials, case–control studies and cohort studies were eligible for inclusion. Editorials, opinion pieces and review articles were not considered. Studies were not limited based on year of publication or geographic location. Included texts were limited to those published in the English language and studies without a full text were excluded. Where there was overlap in patient data between studies, the study with larger patient numbers was included.

2.3 | Data items, synthesis of results and quality appraisal of included studies

After performing the final search and following removal of duplicates, studies were screened by title and abstract. Studies deemed eligible for full-text review were screened for reporting on the extent of surgical resection in ATC by two reviewers (E.F.C. & T.J.C.). Where disputes existed between reviewers over a particular study's inclusion, a third reviewer arbitrated (J.H.). The following study characteristics were collected from included studies: (1) study year, (2) study location, (3) study design, (4) number of patients with ATC, (5) ATC staging information as per the staging used at time of study, (6) number of male and female patients, (7) age of included patients, and (8) patient treatment strategy. The following outcome reporting was also collected where provided: (1) extent of surgical resection for ATC/definition of an unresectable tumor (if provided), (2) resection margin status, (3) OS reported following ATC resection, and (4) postoperative morbidity following ATC resection. The quality of studies was assessed using the National Institute of Health/National Heart, Lung, and Blood Institute (NIH/NHLBI) Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.[15] Data from included studies were thematically separated into: study characteristics, extent of surgical resection, other non-surgical treatment, postoperative outcomes (margin status and OS), as well as postoperative morbidity. It was not possible to perform meta-analysis due to the heterogeneity in the reporting of outcomes, extent of surgical resection and the approach to the definition of unresectable tumors.

3 | RESULTS

3.1 | Study selection

The final search returned 6901 articles. References were firstly downloaded from each database and screened for duplicates using both manual and automated processes. Following the removal of duplicates

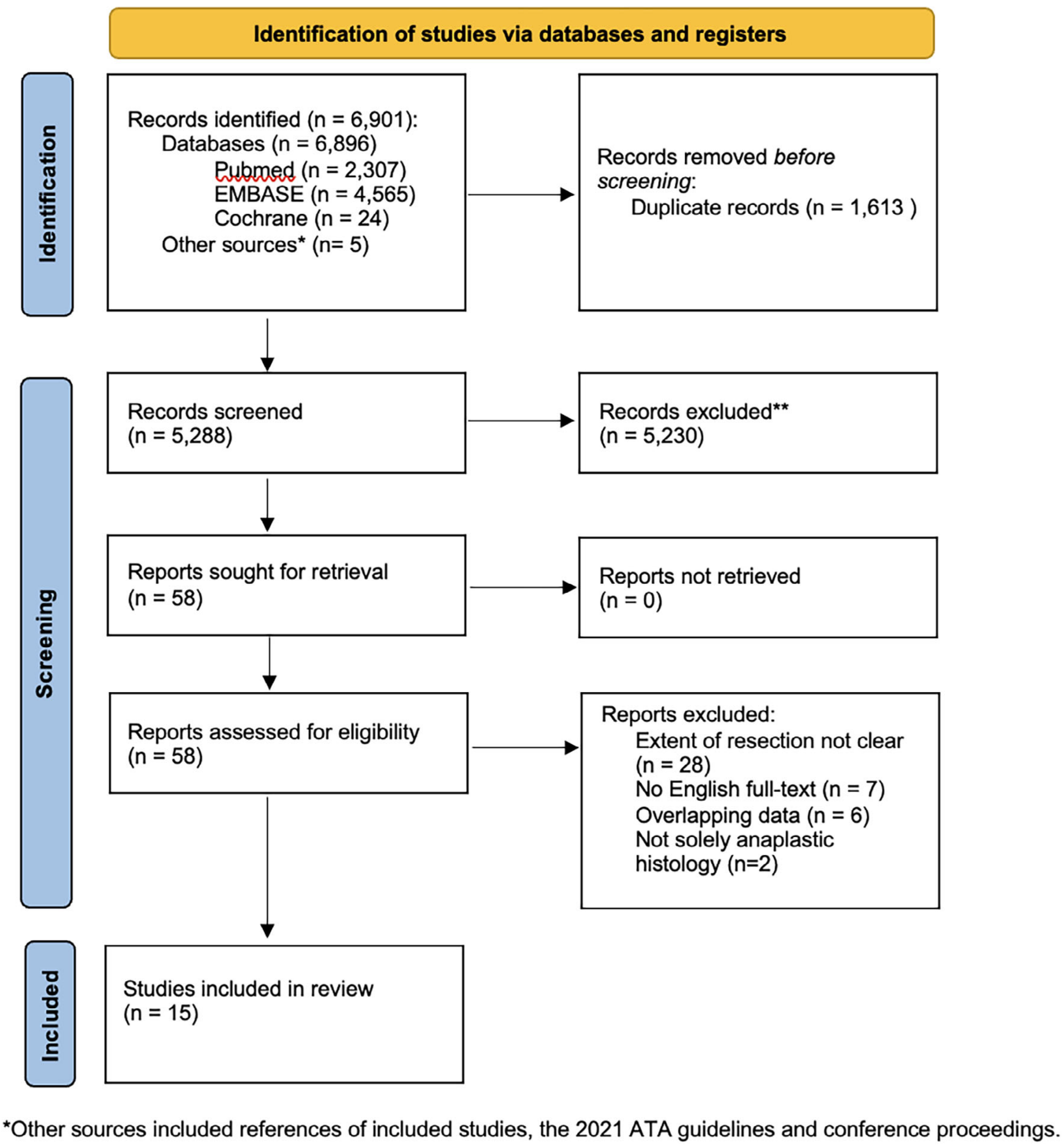

FIGURE 1 PRISMA flow diagram.

TABLE 1 Characteristics of included studies.

Study	Year	Design	Location	Patients/staging	Male/female	Age
Zhao	2023	Retrospective single center	USA	44 patients 18 (40.9%)—IVB 26 (49.1%)—IVC	22 (50.0%) males 22 (50.0%) females	Mean 63.4 years
McCrary	2022	Case series	USA	4 patients 1 (25.0%)—IVA 3 (75.0%)—IVB	2 (50.0%) males 2 (50.0%) females	Mean 65.5 years
Flukes	2021	Retrospective single center	USA	5 patients 5 (100%)—IVB/IVC	NR	NR
Zheng	2021	Case report	China	1—IVB	1—female	55 years
Wachter	2020	Retrospective multicenter	Germany	42 patients 2 (4.8%)—IVA 22 (52.4%)—IVB 18 (42.8%)—IVC	23 (54.8%) males 19 (45.2%) females	69 years (range 33–89 years)
Baek	2016	Retrospective multicenter	South Korea	329 patients 57 (17.3%)—IVA 163 (49.5%)—IVB 103 (31.3%)—IVC	118 (35.9%) males 211 (64.1%) females	NR
Lee	2015	Retrospective single center	South Korea	98 patients 45 (45.9%)—T4b 69 (70.4%)—Node + 20 (20.4%)—IVC	53 (54.1%) males 45 (45.9%) females	Mean 63.5 years ±13.4 years (SD)
Sugitani	2014	Retrospective multicenter	Japan	546 patients 77 (14.1%)—IVA 233 (42.6%)—IVB 223 (40.8%)—IVC 13 (2.4%)—Unknown	IVB patients 74 (31.8%) males 150 (64.4%) females	Mean 69.2 years ±11.3 years (SD)
Brignardello	2014	Retrospective single center	Italy	55 patients 41 had surgery 17 (41.5%)—IVB 24 (58.5%)—IVC	21 (38.1%) males 34 (61.9%) females	Median 73.2 years (IQR 64.6–79.2 years)
Aslan	2014	Retrospective single center	Mexico	29 patients 3 (10.3%)—IVA 18 (62.1%)—IVB 8 (27.6%)—IVC	8 (27.6%) males 21 (72.4%) females	Mean 64.5 years (range 35–91 years)
Brown	2013	Retrospective single center	USA	38 patients 16 (42.1%) resectable IVA/IVB 4 (10.5%) unresectable IVB 18 (47.4%)—IVC	21 (55.3%) males 17 (44.7%) females	Mean 64.5 years (range 32–87 years)
Ito	2012	Retrospective single center	Japan	40 patients 25 (62.5%) – IVB 15 (37.5%) – IVC	14 (35.0%) males 26 (65.0%) females	Mean 72.2 years (range 52–84 years)
Akaishi	2011	Retrospective single center	Japan	100 patients 11 (11.0%)—IVA 31 (31.0%)—IVB 58 (58.0%)—IVC	20 (20.0%) males 80 (80.0%) females	NR
Haigh	2001	Retrospective single center	USA	33 patients 24 had surgery 20 (83.3%) stage IVB/IVC	13 (39.4%) males 20 (60.6%) females	Mean 69 years (range 47–80 years)
Passler	1999	Retrospective single center	Austria	120 patients 23 (19.2%)—IVA 43 (35.8%)—IVB 94 (78.3%) extrathyroidal extension 44 (36.7%) Node + 54 (45.0%)—IVC	43 (35.8%) males 77 (64.2%) females	NR

Abbreviations: ATC, anaplastic thyroid cancer; IQR, interquartile range; NR, not reported.

5288 articles were screened for eligibility based on their title and abstract resulting in the exclusion of 5230 records. The remaining 58 studies were then sought for full-text retrieval. Twenty-one studies met criteria for inclusion in the final review.[5,12,16–34] However, six further studies were subsequently excluded due to overlapping patient data[5,12,28,32–34] leaving 15 studies to be included in the final review[16–27,29–31] (Figure 1).

3.2 | Study characteristics

Of the 15 studies included in this review, the year of publication ranged from 1999 to 2023.[16–27,29–31] Eight countries were represented across the 15 included studies. Twelve studies included patients from a single center[16–23,27,29–31] while three studies were multicenter.[24–26] Overall, 1484 patients were included with the number of patients

TABLE 2 Structures included in resection of disease.

Study	Thyroid + ND	Larynx ± pharynx	Trachea	Esophagus	Other[a]	Mets
Zhao 2023	+	+	+	− Muscularis layer resection only	+ RLN CN XI/XII IJV Superior mediastinal resection	−
McCrary 2022	+	−	−	−	−	−
Flukes 2021	+	+	−	+	−	−
Zheng 2021	+	−	−	−	−	−
Wachter 2020	+	−	−	−	−	+
Baek 2016	+	+	+	+	+ Common carotid IJV Mediastinal resection	−
Lee 2015	+	+	+	+	+ Carotid IJV	−
Sugitani 2014	+	+ (only in super-radical)	+ (only in super-radical)	+ (only in super-radical)	+ Mediastinal resection RLN IJV	−
Brignardello 2014	+	− Muscular layer resection only	−	− Muscularis layer resection only	+ IJV RLN CN X Phrenic nerve Mediastinal resection	−
Aslan 2014	+	+	−	−	+ IJV CN XI	−
Brown 2013	+	+	+	+	−	−
Ito 2012	+	+	+	+	+ IJV RLN	−
Akaishi 2011	+	−	+	+	−	−
Haigh 2001	+	−	−	−	+ RLN	−
Passler 1999	+	−	+	+	+ IJV	−
Total	15/15 (100%)	8/15 (53.3%)	8/15 (53.3%)	8/15 (53.3%)	−	1/15 (6.7%)

Abbreviations: CN, cranial nerve; IJV, internal jugular vein; Mets, metastases; ND, neck dissection; RLN, recurrent laryngeal nerve.

[a]Other structures resected named with each study.

TABLE 3 Extent of surgical resection and overall treatment.

Study	Year	Definition of resectable/unresectable	Other treatment
Zhao	2023	Unresectable 360-degree carotid encasement, innominate artery encasement, prevertebral fascia involvement, floor of neck or brachial plexus involvement	Neoadjuvant group ($n = 32$) BRAF/MEK inhibition ± anti PD-L1 -Median reduction in tumor size 61% Upfront surgery ($n = 12$) Adjuvant BRAF/MEK inhibition ± anti PD-L1
McCrary	2022	2 (50.0%) patients underwent surgical resection Not considered for surgery -Medical comorbidities -Extensive tracheal/esophageal invasion, or prevertebral involvement -Metastatic disease (stage IVC)	Patient 1 neoadjuvant (3 months preop) Dabrafenib/ Trametinib (BRAF V600E mutation) Adjuvant targeted therapy plus CRT Patient 2 adjuvant Pembrolizumab/Lenvatinib (BRAF V600E negative)
Flukes	2021	Only included patients undergoing laryngectomy, pharyngolaryngectomy or pharyngolaryngooesophagectomy because of locally advanced ATC	NR
Zheng	2021	Did not consider resection of tissues other than thyroid or nodal disease	Adjuvant Apatinib and Camrelizumab plus RT
Wachter	2020	Curative intent surgery 21/24 (87.5%) stage IVA/IVB—thyroidectomy ± ND 9/18 (50.0%) stage IVC—local resection + resection of metastases	Surgery only 7/21 (33.3%) Adjuvant CRT in 14/21(66.7%) curative intent patients
Baek	2016	188 curative intent resections Thyroidectomy + ND plus Tracheal resection, laryngectomy/ laryngopharyngectomy, esophageal resection ± free flap reconstruction, mediastinal resection, carotid artery resection and reconstruction	Surgery only 94/188 (50.0%) Curative resection and adjuvant RT/concurrent CRT 84/188 (44.7%) Curative resection and adjuvant CT 10/188 (5.3%)
Lee	2015	50 patients deemed resectable Unresectable tumor Tumor invading extensively into the laryngotracheal, esophageal or prevertebral space, the carotid arteries or IJV which could not be resected even with aggressive surgery	19/50 (38.0%) surgery only 31/50 (62.0%) surgery plus adjuvant RT
Sugitani	2014	144 stage IVB patients treated surgically 23/144 (16.0%) underwent super-radical surgery TT + ND plus total laryngectomy/pharyngolaryngectomy, tracheal resection, esophageal resection, mediastinal resection 49/144 (34.0%) restricted radical surgery -curative resection by means of thyroidectomy + cervical lymph node dissection ± resection of the muscles, veins, RLN, and/or superficial shaving of the aerodigestive tract	96/144 (66.7%) adjuvant RT 69/144 (47.9%) adjuvant CT
Brignardello	2014	41 patients' curative intent surgery 14 deemed non resectable -Short life-expectancy -Overt invasion of hypopharynx, esophagus, larynx, and/or trachea, involvement of vascular structures of the mediastinum, or prevertebral fascia and paraspinous muscles *Stage IVC NOT a contraindication for surgery	Surgery alone 5/41 (12.2%) Surgery plus CT 12/41 (29.3%) Surgery plus CRT 24/41 (58.5%)
Aslan	2014	Curative intent surgery in 16 patients 13 patients were considered non-resectable Presence of extensive extrathyroidal disease that affected the trachea, mediastinum vessels, cervical esophagus, prevertebral fascia, or poor functional health	Surgery only 2/16 (12.5%) Surgery plus CRT 14/16 (87.5%)

TABLE 3 (Continued)

Study	Year	Definition of resectable/unresectable	Other treatment
Brown	2013	16 patients underwent curative intent resection Unresectable -Stage IVC -Local tumor extent lateral to the carotid	Surgery only 2/16 (12.5%) Surgery plus CRT 14/16 (87.5%)
Ito	2012	IVB unresectable -Tumor invaded the prevertebral fascia, mediastinal vessels, or encased the carotid artery	Surgery alone 2/12 (16.7%) Surgery plus RT 10/12 (83.3%)
Akaishi	2011	70 patients underwent surgery -Extensive surgery in 9 patients Unresectable -Extent of extrathyroidal invasion such as that involving the esophagus and the carotid artery	Surgery plus adjuvant RT 60/70 (85.7%) Surgery plus adjuvant CT 25/70 (35.7%)
Haigh	2001	26 patients treated with neck exploration Potentially curative surgery Resection of all visible disease including leaving minimal residual disease adherent to structures such as the RLN, carotid artery, trachea, or esophagus	Surgery only 2/26 (7.7%) Surgery plus RT, CT or both 24/16 (92.3%)
Passler	1999	120 patients underwent surgery Curative intent surgery: thyroidectomy + ND plus: removal part of the straight neck muscles, tracheal wall resections, esophageal wall resections, IJV resections	RT 13/120 (10.8%) CT 4/120 (3.3%) CRT 9/120 (7.5%) *No information on adjuvant therapy for 47 patients (39.2%)

Abbreviations: ATC, anaplastic thyroid cancer; CT, chemotherapy; CRT, chemoradiotherapy; IJV, internal jugular vein; ND, neck dissection; NR, not reported; RT, radiotherapy; RLN, recurrent laryngeal nerve.

included in each study ranging from 1 to 546 patients. Fourteen studies reported the sex of included patients with the majority of included patients being female (64.4%).[16–26,29–31] Within the 11 studies providing the age of included patients, the mean or median age ranged from 55.0 to 73.2 years (Table 1). Quality assessment of included studies is provided in Data S1.

3.3 | Extent of surgical resection

A total of 765 patients (51.5%) underwent attempted curative intent surgery. The extent of surgical resection in ATC varied between studies (Table 2). All studies utilized the anatomical extent of disease when considering the appropriateness of surgical resection (Table 3). There was consensus in all studies that thyroid resection and neck dissection was appropriate in the management of ATC (Table 2). The approach to resection of adjacent tissues varied between studies. Eight studies considered laryngeal ± pharyngeal resection (8/15, 53.3%), eight studies (53.3%) considered tracheal resection and again eight studies (53.3%) considered esophageal resection (Table 2). Some studies also detailed resection of other locoregional structures, such as the recurrent laryngeal nerve, internal jugular vein and mediastinal structures (Table 2). There was an agreement among most studies that carotid artery encasement, mediastinal vessel involvement and prevertebral fascia involvement denoted unresectable disease (Table 3). The studies by Lee et al. and Baek et al. attempted carotid artery resection with reconstruction at time of surgery.[23,25] Two studies provided a contrasting definition of 'unresectable' disease and the extent of resections performed (i.e., esophageal/pharyngeal disease was deemed unresectable despite esophageal or pharyngeal resection being performed with curative intent in the study group) (Tables 2 and 3).[16,19] Three studies considered patient factors regarding the appropriateness of surgical resection, detailing that those with a short life-expectancy or poor functional status were deemed 'unresectable' due to patient factors.[16,22,29]

3.4 | Other treatment

Fourteen studies (93.3%) described the neoadjuvant or adjuvant treatment received by patients in addition to surgery.[16–26,29–31] Curative intent treatment largely incorporated surgery followed by adjuvant radiotherapy with or without chemotherapy in all of these studies (Table 3). In addition to this, three studies (3/15, 20.0%) detailed adjuvant targeted therapy with or without immunotherapy.[29–31] Two studies (2/15, 13.3%) considered neoadjuvant targeted therapy prior to surgical resection[29,31] (Table 3). Patients in these studies were stage IVB or stage IVC (Table 1). Extent of primary tumor following neoadjuvant targeted therapy dictated appropriateness for surgical resection in these studies. Surgical resection in these instances typically included thyroidectomy and neck dissection (Table 2). The study by Zhao et al. demonstrated less 'extensive' resections using the thyroid neck morbidity complexity scoring system and a lower tumor following neoadjuvant targeted treatment.[31]

TABLE 4 Postoperative outcomes and morbidity.

Study	Year	Postoperative outcomes	Postoperative morbidity
Zhao	2023	Neoadjuvant therapy ($n = 32$) 19/32 (59%) had an ATC pathologic complete response. 1y OS—93.6% (CI 84.9–100) 2y OS—80.3% (CI 66.1–94.5) Upfront surgery ($n = 12$) 1y OS—74.1% (CI 48.7–99.5) 2y OS—74.1% (CI 48.7–99.5)	Only presented for post neoadjuvant targeted therapy groups ($n = 32$) 2/32 (6.3%) Neck abscess 1/32 (3.1%) Ischaemic stroke day 1 postop 1/32 (3.1%) Readmission with hypothyroidism
McCrary	2022	Patient 1: Almost total disease resolution Patient 2: 5 m OS with response of disease to adjuvant targeted therapy *Died at 5 m secondary to red cell aplasia as a result of pembrolizumab	None
Flukes	2021	All 5 patients died within 2 years	NR
Zheng	2021	Patient alive with locoregional recurrence at 11 m	None
Wachter	2020	Resection IVA 2/2 (100.0%) R0 IVB 4/22 (18.2%) R0; 18/22 (81.8%) R1/2 Survival IVA 2/2 (100.0%) OS >36 m IVB: median OS 16 m if R0 resection; 5.5 m if R1 resection ($p = 0.63$)	NR
Baek	2016	Median OS by treatment ($p < 0.01$) Non-operative ($n = 141$) -Palliation ($n = 81$)—2 m -CRT ($n = 50$)—5 m -CT ($n = 10$)—3 m Operative patients ($n = 188$) Surgery only 94/188 (50.0%)—7 m Surgery plus CRT 84/188 (44.7%)—15 m Surgery plus CT 10/188 (5.3%)—5 m	NR
Lee	2015	On multivariate analysis OS significantly reduced for -unresectable tumor (OR = 1.39 [CI 1.21–1.74]) -tracheal invasion (OR = 4.45 [CI 2.32–9.33])	NR
Sugitani	2014	Median OS ($p \leq 0.001$) -No surgery 3.3 m -Debulking surgery 4.3 m -Restricted radical surgery 10.5 m -Super radical surgery 4.3 m 6-month CSS ($p \leq 0.05$) -No surgery 22/80 (27.5%) -Debulking surgery 31/72 (43.1%) -Restricted radical surgery 33/49 (67.3%) -Super radical surgery 9/23 (39.1%) 1-year OS ($p \leq 0.05$) -No surgery 6/80 (7.5%) -Debulking surgery 9/72 (12.5%) -Restricted radical surgery 19/49 (38.8%) -Super radical surgery 7/23 (30.4%)	Need for tracheostomy No tracheostomy -No surgery 53/80 (66.3%) -Debulking surgery 46/72 (63.8%) -Restricted radical surgery 41/49 (83.7%) -Super radical surgery 2/23 (8.7%) Permanent tracheostomy -No surgery 22/80 (27.5%) -Debulking surgery 22/72 (30.6%) -Restricted radical surgery 7/49 (14.3%) -Super radical surgery 18/23 (78.2%)
Brignardello	2014	Stage IVB ($n = 24$) median OS -Eligible for surgery (17/24) 6.4 m (95% CI 3.94–11.9 m) -Not eligible for surgery (7/24) 1.5 m (95% CI 0.5–7.7 m) Overall median OS ($p \leq 0.05$) Maximal debulking ($n = 29$) 6.6 m Partial debulking ($n = 12$) 3.3 m	2/41 (4.9%) RLN injury 9/41 (22.0%) hypocalcaemia. 1/41 (2.4%) blood transfusion 1/41 (2.4%) reintubation 1/41 (2.4%) pulmonary embolism 4/41 (9.8%) patients required tracheostomy
Aslan	2014	The mean OS for the whole group was 119 days (95% CI, 36.3–201.6 days).	NR

TABLE 4 (Continued)

Study	Year	Postoperative outcomes	Postoperative morbidity
Brown	2013	7/14 (50.0%) OS with complete surgical resection followed by RT (follow-up range 9 m—8 years) 6/14 (42.9%) developed distant metastases (range 2–4.8 m) *No follow-up survival data for 2 patients	2/12 (16.7%) total laryngectomy patients developed pharyngocutaneous fistulas 9/16 (56.3%) temporary hypocalcaemia 5/16 (31.3%) permanent hypocalcaemia 1/16 (6.3%) myocardial infarction All survivors ($n = 7$) are currently eating and drinking.
Ito	2012	Resection in 'resectable' IVB ($n = 12$) tumors 2/12 (16.7%) R1 10/12 (83.3%) R2 Median OS ($p \leq 0.05$) -Resectable IVB ($n = 12$) 9.6 m -Unresectable IVB ($n = 13$) 4.0 m -IVC ($n = 15$) 4.2 months	NR
Akaishi	2011	Median OS ($p \leq 0.05$) -IVA ($n = 11$) 33.5 m -IVB ($n = 31$) 6.1 m -IVC ($n = 58$) 2.5 m 6-month OS ($p \leq 0.05$) R0 resection 16/24 (67.8%) R1/R2 resection 21/46 (45.6%) No surgery 3/30 (10.0%) 1-year OS ($p \leq 0.05$) R0 resection 13/24 (54.2%) R1/R2 resection 8/46 (17.4%) No surgery 1/30 (3.3%)	NR
Haigh	2001	Median OS ($p \leq 0.05$) -No/minimal residual disease ($n = 8$) 43 m -Gross residual disease ($n = 18$) 3 m OS for patients with gross residual disease = OS for patients receiving CRT ($p = 0.63$).	1/26 (3.8%) wound infection and dehiscence 1/26 (3.8%) ICU admission for respiratory compromise
Passler	1999	Resection R0–44/120 (36.7%) R1/R2–76/120 (63.3%) Median OS ($p \leq 0.001$) -Overall—3.1 m -R0 resection ($n = 29$) 6.1 m -R1/R2 resections ($n = 76$) 2.2 m	(22.2%) RLN injury 2/120 (1.7%) wound hematomas 2/120 (1.7%) wound infection 10/120 (8.3%) permanent hypocalcaemia 3/120 (2.5%) pulmonary complications (one of which was fatal)

Note: R0: complete resection with microscopically uninvolved margins; R1: complete resection of gross disease with microscopically positive margins; R2: grossly incomplete resection.
Abbreviations: CRT, chemoradiotherapy; CSS, cause specific survival; CT, chemotherapy; 95% CI, 95% confidence interval; NR, not reported; m, months; OR, odds ratio; OS, overall survival; RLN, recurrent laryngeal nerve; RT, radiotherapy.

3.5 | Postoperative outcomes

The reporting of survival outcomes in the included studies varied (Table 4). In studies with patients receiving conventional treatment strategies (surgery ± chemoradiotherapy), overall median OS was consistently reported as <9 months, irrespective of the extent or limits of surgical resection. An initial R0 resection was associated with significantly improved OS in four studies (Table 4).[19–21,26] For example, the study by Akaishi et al. demonstrated a 1-year OS of 54.2% (13/24) with an R0 resection versus 17.4% (8/46) with an R1/R2 resection.[19] Lee et al. demonstrated tracheal invasion as the strongest negative anatomical prognosticator for OS (OR of death = 4.45 [CI 2.32–9.33]).[23] Sugitani et al. provided survival information based on the 'radicalness' of resection (defined in Table 3). Patients undergoing "super-radical" surgery (i.e., resection of the larynx, pharynx, esophagus, trachea or mediastinal structures) demonstrated a similar median OS and 6-month cause-specific survival to patients undergoing debulking surgery or no operative management, and a significantly worse median OS and 6-month cause-specific survival to those undergoing 'restricted radical' surgery[24] (Table 4). Studies also demonstrated that OS improved in patients with lower disease stage and those undergoing surgical resection within a multimodal treatment framework.[16,18,19,25,26] The OS of patients in the studies utilizing targeted therapy along with surgical resection was consistently greater than those in studies not utilizing targeted therapy (Table 4).[29–31] For example, the largest study to evaluate neoadjuvant targeted therapy followed by surgical resection demonstrated a 1-year OS of 93.6% (CI 84.9–100) and a 2-year OS of 80.3% (CI 66.1–94.5).[31]

3.6 | Postoperative morbidity

Eight out of the 15 included studies (53.3%) provided details pertaining to postoperative surgical morbidity[16,17,20,21,24,29–31] (Table 4). Sugitani et al. demonstrated that the majority undergoing 'super-radical' surgery were likely to require a tracheostomy postoperatively (21/23, 91.3%) with 18 (85.7%) of these patients needing a permanent tracheostomy. The rate of tracheostomy was significantly lower in patients undergoing no surgery (27.5%), debulking surgery (30.6%) or restricted radical surgery (14.3%).[24] Other reported postoperative complications included recurrent laryngeal nerve injury, pharyngocutaneous fistula (following laryngectomy), hypocalcaemia, wound infection and pulmonary compromise[16,17,20,21,24,29–31] (Table 4).

4 | DISCUSSION

We highlight considerable variability in the approach to surgical resection of patients with ATC in this scoping review of 15 studies. There was agreement in all studies that resection of intrathyroidal tumors (stage IVA) and locoregional lymphadenopathy was appropriate and improves OS. However, it is evident that the determination of ATC resectability in stage IVB disease is not uniform among surgeons leading to variability in the real-world management of this disease. Eight studies considered laryngeal ± pharyngeal resection (which the 2021 ATA guidelines specifically recommend avoiding) (53.3%), eight studies (53.3%) performed tracheal resection and eight studies (53.3%) performed esophageal resection. These surgeries represent major resections exposing patients to significant operative risk which may not be in the patients best interest given the limited life expectancy of many patients with ATC. Postoperative morbidity was a poorly reported outcome within the present analysis, only reported in eight of the 15 studies (53.3%). Notably, it would appear that the use of neoadjuvant targeted therapy significantly downstages locally advanced disease, affords less extensive resection with the potential of reduced postoperative morbidity as evident in the study by Zhao et al.[31]

Evidence in support of up front surgical resection for stage IVA ATC is unequivocal with an R0 resection offering the best chance of long-term survival.[9] However, the impact surgical resection has in stage IVB disease is less clear. In stage IVB disease OS was similar between studies utilizing conventional treatment strategies irrespective of the surgical margin obtained.[26,35] A limitation of studies investigating the impact of surgical resection and/or margin status on survival in stage IVB ATC is the vastly heterogenous patient cohort. Stage IVB ranges from minimal extrathyroidal extension or intrathyroidal ATCs with small volume nodal disease to gross macroscopic invasion of the esophagus, trachea, larynx or prevertebral fascia by tumor or nodal disease.[8] Surgical resection may range from a total thyroidectomy and central compartment neck dissection for low volume disease to a total thyroidectomy, bilateral neck dissection, and pharyngolaryngo-oesophagectomy for large volume disease. The potential for starkly different disease burdens and expected prognoses under the same staging category suggests that further staging criteria may be required to guide surgical treatment in the targeted therapy era. Only one study equated the extent of surgical resection with OS within the present scoping review.[24] Sugitani et al. reported that 'super-radical' surgery incorporating either pharyngolaryngeal, tracheal, esophageal or mediastinal resection offered the same OS and 6-month cause specific survival as no surgery or palliative surgery and worse OS in comparison to 'restricted radical' surgery.[24] One may consider that this reflects the more advanced disease stage of those patients undergoing 'super-radical' surgery. Additionally, a significantly higher proportion of 'super-radical' patients were permanently tracheostomy dependent post-operatively.[24] Another important consideration demonstrated in the present analysis is the greater than four times risk of mortality among ATC patients with tracheal invasion demonstrated by Lee et al.[23] These limited findings would appear to suggest that aggressive resection of locoregional structures does not confer benefit to patients in the context of stage IVB ATC. Notably, despite the less extensive resections among the studies utilizing targeted therapy, patients in these studies demonstrated improved OS.[29–31] This again would favor that patients where possible are treated with up front neoadjuvant targeted therapeutics and reassessed following treatment for consideration of surgery.

The present scoping review raises several questions. First, at present, non-surgical initial treatment strategies appear to be most appropriate in the management of extrathyroidal ATC where possible. Recent evidence has demonstrated considerably improved outcomes in *BRAF V600E* mutated patients undergoing neoadjuvant targeted therapy followed by surgical resection. However, only 30% to 40% of patients with ATC will have a *BRAF* mutation and concerns exist as resistance has been demonstrated following initial response to *BRAF* therapy in ATC.[36,37] While other targetable mutations in ATC have been demonstrated as well as immunotherapy usage, these therapeutic options are less well established and their use remains under investigation. This review highlights the need for clearer definitions of surgical resectability than is currently offered by the present AJCC staging and ATA guidelines.[7,8] Given the lack of clarity in the literature regarding what resections have been attempted and what extent of disease patients have preoperatively, especially in stage IVB disease, it is not possible to contextualize the impact of surgical resection in this heterogenous cohort. Given the strong evidence supporting targeted therapy in ATC, it is crucial for clinicians to understand which patients should be considered for surgical resection following neoadjuvant targeted therapy, particularly as this will largely entail patients (advanced stage IVB and stage IVC) previously considered unresectable by many. In addition, those not eligible for neoadjuvant therapy who may benefit from surgical resection will need to be more clearly defined. Given the low incidence of these tumors, and poor reporting of the extent of resection in the literature, clinical consensus may be the most appropriate methodology to define the limits of resection in ATC or indeed the reporting of surgical resection in ATC.

As with all studies the present scoping review is subject to limitations. First, the studies included are largely retrospective and small in nature which is not unexpected given the rarity of ATC. Thus, they are subject to confounding, selection, and ascertainment biases. Second, every effort has been made by the authors to conduct a comprehensive search in an effort to minimize selection bias within the present review. Finally, meta-analysis of data was prohibited by study reporting, definitions of resection, and outcomes heterogeneity, as well as the lack of control or comparator groups in a number of studies.

In conclusion, the definition of surgically resectable disease in ATC is poorly defined in the literature, particularly for locoregionally advanced disease. Given the current available evidence, extensive resection of locoregional structures does not appear to be of benefit in the management of extrathyroidal ATC. Neoadjuvant targeted therapy followed by surgical resection may allow less extensive surgery while providing superior OS in comparison to upfront surgical resection followed by chemoradiotherapy in extrathyroidal ATC. Thus, neoadjuvant targeted therapy in appropriately selected cases should become standard of care in BRAF mutated stage IVB disease similar to the treatment algorithm in MD Anderson Cancer Centre's FAST clinic, which differs from ATA guidance regarding 'resectable' stage IVB disease.[5,8] However, surgical resection still maintains a critical role in management of this disease and in the era of targeted therapy, a robust, clear, and transparent definition of resectable disease in ATC is necessary. This will allow clinicians to better select patients who will benefit from surgical intervention following neoadjuvant treatment as well as those not eligible for targeted treatment undergoing upfront resection. Given the rarity of ATC and lack of available evidence in this regard, clinical consensus appears to be the optimal and only feasible strategy to provide this clarity and afford the ability to improve the literature in this poorly reported area.

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CONFLICT OF INTEREST

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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