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Research Article

Neoadjuvant Targeted Molecular Therapy Facilitates Surgery in Locally Advanced Thyroid Cancer

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Abstract

Introduction: Locally advanced thyroid cancer presents significant therapeutic challenges, particularly when tumours exhibit aggressive biology and invade critical structures, rendering them unresectable at presentation. This study evaluates the efficacy of neoadjuvant multikinase inhibitor therapy in enhancing surgical resectability in patients with locally advanced disease.

Methods: A retrospective review was conducted on patients with locally advanced, unresectable thyroid cancer treated between January 2017 and December 2022. Multidisciplinary team assessment identified seven patients, of whom five received lenvatinib with three-monthly follow-up. Treatment response was evaluated using RECIST criteria, and outcomes included therapy safety, progression to surgery, and overall survival.

Results: Five patients with cT3/T4 disease were treated with neoadjuvant lenvatinib and achieved objective response to treatment with significant reduction in tumour size (mean 30.5 ± 17.4%). Four patients proceeded to surgery achieving a 50% R1 and 50% R2 resection rate. Adverse events were mild or moderate, and resolved with dose reduction or when neoadjuvant therapy was withheld pre-operatively. To date three patients who underwent surgery are alive with a median follow up of 44.7 months (range 30.1-53.3 months), with one death from distant disease 13 months after diagnosis.

Conclusion; In this small series, neoadjuvant lenvatinib therapy demonstrated effective antitumour activity in LATC and facilitated surgical resection.

INTRODUCTION

Thyroid cancer is a common endocrine malignancy with approximately 4,100 cases diagnosed in Australia in 2023, accounting for 0.25 per cent of new cancer diagnoses [1]. Despite the increase in incidence, mortality rates remain less than 0.5 per 100 000, reflecting a generally favourable prognosis [1]. However, 2-4.1% of patients present with locally advanced thyroid cancer (LATC) with invasion of critical structures such as the trachea, oesophagus or major blood vessels [2-4]. LATC is commonly associated with hobnail and tall cell variants of papillary thyroid cancer (PTC), poorly differentiated thyroid cancer (PDTC), medullary thyroid cancer (MTC) and anaplastic thyroid cancer (ATC) [5,6]. Regardless of the histological type, LATC has an increased incidence of locoregional recurrence and distant metastases [7,8]. Amongst patients with LATC, local complications including tumour invasion causing airway obstruction, and massive haemorrhage from trachea-oesophageal fistula were amongst the most common causes of death [9].

Although primary surgical resection remains the cornerstone of LATC management, there is increased focus on reducing surgical morbidity and mortality. The role of tyrosine kinase inhibitors (TKI) in advanced thyroid cancer has evolved beyond adjuvant systemic therapy for metastatic disease [10,11]. Their use in the neoadjuvant setting to downstage the tumour in anticipation of surgical resection has marked a significant shift in the treatment approach for LATC [12]. Case reports of neoadjuvant therapy targeting molecular drivers including *BRAF* ^{V600E}, *RET, NTRK* and *ALK* show promise, enabling less extensive surgery, reduced incomplete resection, as well

as providing important prognostic information through assessing pathological response to therapy [13-16].

Lenvatinib is a multikinase inhibitor (MKI) with anti-tumour activity used in the treatment of several cancers including differentiated thyroid cancer, renal cell carcinoma, melanoma and hepatocellular carcinoma [17]. Its broad anti-tumour and anti-angiogenic activity occur due to potent inhibition of phosphorylation and activation of tyrosine kinases including vascular endothelial growth factor receptors (VEGFR) 1-3, fibroblast growth factor receptors (FGFR) 1-4, platelet-derived growth factor receptor (PDGFR) alpha, c-KIT and the RET proto-oncogene [18,19]. The over-expression or activation of these signalling proteins in thyroid malignancy is associated with tumour proliferation and metastasis [20-23]. Since first use in 2017, lenvatinib has demonstrated efficacy in improving progression free survival in radioiodine refractory DTC, as well as MTC and ATC [24-27]. Despite the promising results of lenvatinib and other TKIs, neoadjuvant targeted therapy is not yet considered standard treatment for LATC. Further research is necessary to guide recommendations and real-world changes to management.

This study describes the experience of a quaternary referral centre in Australia with neoadjuvant lenvatinib in patients presenting with unresectable LATC.

METHODS

Case data were prospectively collected on five patients with LATC treated at a tertiary referral centre from January 2017 to December 2022. All cases were reviewed by the Endocrine Tumour Multidisciplinary Team (MDT), comprised of endocrinologists, endocrine surgeons, anatomical pathologists, radiologists, nuclear medicine physicians and radiation oncologists. Tumour imaging characteristics were assessed by three experienced endocrine surgeons. Patients identified as "surgically non-resectable", "resectable with unacceptable morbidity" or "inoperable due to poor pre-operative functional status" were considered for neoadjuvant MKI therapy. Immunohistochemistry and molecular testing were conducted to identify targetable mutations, including *BRAF* ^{V600E}, *RET, NTRK* and *ALK*, and patients who received neoadjuvant BRAF / MEK inhibitor therapy were excluded. Ethics approval was granted from the Northern Sydney Local Health District Human Research Ethics Committee (#2020/ETH02787) and participants provided informed consent.

Selected patients were commenced on 24mg of lenvatinib daily and monitored for potential side effects including hypertension (HTN), arrhythmias, proteinuria, renal dysfunction, fatigue, and bleeding. Mild or moderate adverse reactions were managed with dose reduction while interval breaks were considered in the event of severe side effects. Baseline imaging with high resolution contrast enhanced Computed Tomography (CT) and Positron Emission Tomography (PET) was performed, with CT repeated every three months. Patients were monitored by an endocrinologist and clinical nurse consultant with regular electrocardiograms and biochemical tests, including carcinoembryonic antigen (CEA) and calcitonin for patients with MTC. The MDT determined suitability and timing of surgical resection based on clinical evaluation and radiological response to treatment. If deemed resectable, preoperative laryngoscopy was performed to check vocal cord function.

The primary outcome measure was objective response rate (ORR) according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 [28]. Efficacy was defined as tumour reduction enabling surgical resection. If surgery was unable to be performed, neoadjuvant therapy was considered ineffective [29]. Secondary outcomes measures included completeness of resection R0 (complete), R1 (microscopic residual disease), R2 (macroscopic residual disease), overall survival and safety of therapy. Changes in CEA and calcitonin levels for patients with MTC were also recorded (Table 1).

RESULTS

Between January 2017 and December 2022, a total of 706 PTC, 51 MTC and 8 ATC patients were treated surgically at our institution. Of these, three PTC (0.4%), two MTC (4%) and two ATC (25%) patients were assessed as not surgically resectable at initial presentation. Two PTC patients were commenced on combination BRAF / MEK inhibitor therapy, while the remaining five patients were commenced on neoadjuvant lenvatinib therapy (Figure 1). All patients presented with stage 4 disease with locoregionally advanced tumours, including involvement of adjacent vital structures (trachea, oesophagus, major vessels), bulky / matted lymphadenopathy or distant metastases (4 lung, 2 skeletal, 2 liver). Patient demographics as well as tumour and treatment characteristics are detailed in Table 1 and Table 2. Detailed case descriptions are presented in the Appendix, with patient 2 included in another case series [30].

Histological types receiving neoadjuvant therapy included one PTC, two MTC and two ATC. Associated genomic mutations are presented in Table 1. Patients received a median of 5.5 months of neoadjuvant therapy (range 1.6-8.3). Three patients (60%) achieved a partial

Table 1: Patient demographics and tumour characteristics

Case	1	2	3	4	5
Age at presentation (years) / Sex	76 / F	66 / M	76 / F	66 / M	76 / M
ECOG	1	1	2	0	1
Stage at diagnosis	cT4b N1b M0	cT4b N0 M1	T3a N1b M1	T3a N1b M1	cT4b N1b M1
Histologic type	ATC	ATC	MTC	MTC	PTC
Genetic alteration	*BRAF WT*, somatic *PTEN* and *p53* alteration	*NRAS p.Gln61Arg* and *p.Thr50Ile* (thyroid), *TERT c.-124C>T* (liver)	*RET M918T*	*RET*	*BRAF V600E*
Reason for neoadjuvant therapy	Vascular involvement	Vascular and paravertebral muscle involvement	Poor functional status due to ACTH dependent Cushings	Presence of metastatic distant disease	Vascular and tracheo-esophageal involvement
Metastatic lesions	None	Lung, skeletal	Lung, liver	Lung, liver, skeletal	Lung
Pre-MKI biochemistry	–	–	Calcitonin 958 CEA 340	Calcitonin 3090 CEA 275	–
Pre-operative biochemistry	–	–	Calcitonin 257 CEA 104.5	Calcitonin 299 CEA 64	–
Latest biochemistry	–	–	Calcitonin 59 CEA 14	Calcitonin <5 CEA 6	–
EBRT	Yes	Yes	No	No	Yes
Adjuvant treatment	Lenvatinib	Lenvatinib, pembrolizumab	Selpercatinib	Lenvatinib, selpercatinib	-
Overall survival, status	53.3 months, alive	13 months, deceased	30.1 months, alive	44.7 months, alive	6.5 months, deceased

Table 2: Neoadjuvant therapy and operation details

Case	1	2	3	4	5
Duration of therapy (months)	8.3	6.5	1.6	3	5.5
Side effects of TKI	None	HTN, fatigue, foot ulcers	HTN, mouth ulcers, hand and foot syndrome	None	HTN, fatigue, oral ulcers
RECIST *	9.1% stable disease	52.1% partial response	17.5% stable disease	40.9% partial response	32.8% partial response
Thyroidectomy	Left hemithyroidectomy	Right hemithyroidectomy	Total thyroidectomy	Total thyroidectomy	N/A (progression distant disease)
Neck dissection	Bilateral CND	Bilateral CND, R LND (III/IV)	Bilateral CND, L LND (II-V), R LND (III/IV)	Bilateral CND, L LND (II-V)	-
Sites of ETE	Brachiocephalic vein / SVC, L RLN	Skeletal muscle, trachea, R RLN	Perithyroidal fat	L RLN	-
Resection margin	R2	R2	R1	R1	-
Final histopathology	Poorly differentiated (insular) carcinoma, >95% tumour necrosis	ATC with >90% necrosis	Multifocal MTC	MTC with 50% tumour regression	-

*Change in longest diameter of target lesion

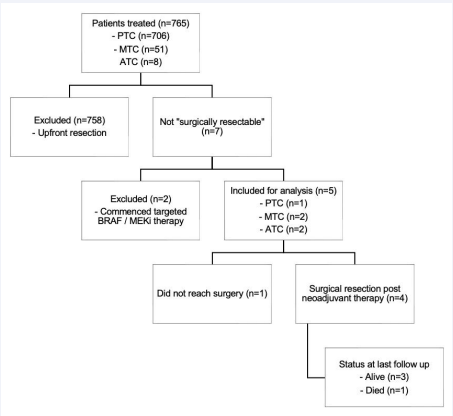

Figure 1 Flowchart outlining management of patient cohort

response and two had stable disease by RECIST 1.1 criteria (Figure 2). The mean best percentage change in the target lesion diameter was a 30.5 ± 17.4% decrease.

Despite local tumour response, the overall results for neoadjuvant lenvatinib were heterogeneous (Table 2). Four patients (80%) proceeded to surgery, whilst the PTC patient did not due to progression of distant metastatic disease. Among patients who underwent surgery, total thyroidectomy was performed for two patients with MTC, while both ATC patients underwent hemithyroidectomy. All patients underwent concurrent central neck dissection with lateral neck dissection performed for patients with involved lateral nodes. One patient required a hemi-sternotomy to resect mediastinal disease and debulk tumour thrombus. No patients required resection of the recurrent laryngeal nerve (RLN), aerodigestive structures or vital vascular structures. No blood transfusion or tracheostomies were performed, and there were no major surgical complications. Lenvatinib was withheld for a median of 11.5 days (range 8-14) before surgery.

The most common adverse events (AE) were HTN (60%), oral ulcers (40%) and hand-foot syndrome (20%). Dose reduction was required for three patients (60%). Post-operatively MKI therapy was continued with lenvatinib monotherapy (n=1), lenvatinib and pembrolizumab (n=1), or selpercatinib (n=2). 3-year overall survival was 60% with a median follow-up period of 30.1 months from diagnosis (range 6.5-53.3 months). To date, three patients are alive and despite evidence of persistent distant metastases on imaging, they remain free of locoregional disease. One patient died due to progressive distant metastases but demonstrated no locoregional recurrence post-operatively.

DISCUSSION

In this case series, we demonstrate the efficacy of neoadjuvant lenvatinib therapy to downstage unresectable LATC, ultimately facilitating surgical resection in four out of five cases (80%).

The use of neoadjuvant TKIs in unresectable LATC is showing promise, with significant radiological response, facilitating the preservation of major neurovascular structures [12-37]. In our series, the aims of commencing neoadjuvant therapy varied among patients. In three cases, this was to achieve local disease control, allowing resection without sacrifice of critical vascular structures and avoiding the need for laryngectomy. In two patients, lenvatinib was initiated with palliative intent to treat distant disease, however its therapeutic effect combined with optimisation of patient comorbidities facilitated subsequent surgery.

As the optimal duration of neoadjuvant MKI therapy has not been established and the durability of treatment response remains unknown, our patients were reviewed every three months to assess treatment response. The MDT recommended surgery as soon as the locoregional disease was considered resectable on imaging, to reduce the risk of developing resistance to pathway inhibition and disease progression. In our series, patients received a median of 5.5 months (range 1.6-8.3 months) of

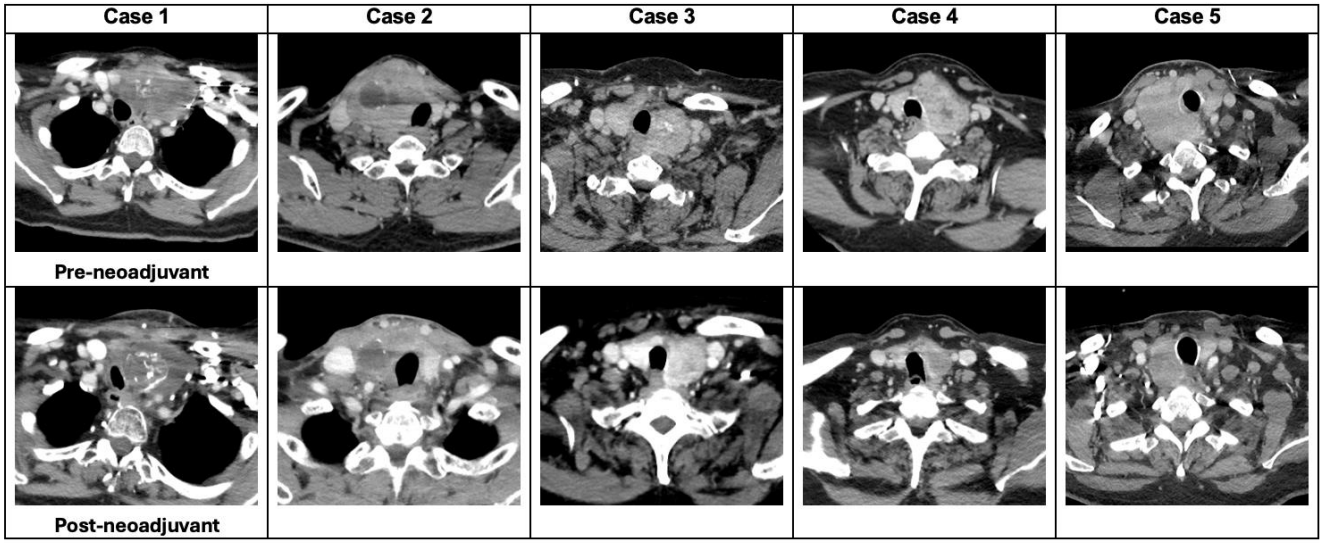

Figure 2 Neck CT before and after neoadjuvant therapy with lenvatinib

neoadjuvant therapy and lenvatinib was typically withheld for a median of 11.5 days (range 8-14 days) before surgery. As TKIs affect the proliferation of endothelial cells and cause adverse effects including HTN, hand-foot skin reactions and thromboembolism. These side effects range in severity and may require dose reduction, interruption or premature cessation of therapy [26-40]. In the SELECT study, across all grades adverse events were reported in 97.3% of patients receiving lenvatinib [24]. Treatment related HTN was the most common treatment related side effect, reported by 60% of patients, followed by oral ulcers (40%) and hand-foot syndrome (20%). This is consistent with previous studies which report a 70% incidence of all grades of HTN [41]. In our series, adverse events were managed with dose reduction and no patients required premature lenvatinib cessation. Although we did not observe increased bleeding during surgery or treatment-related fistula formation, clinicians need to consider the risks of impaired wound healing, haemorrhage and tracheoesophageal fistula formation which have been reported with lenvatinib use [42-46].

Previous case series have demonstrated a survival benefit for neoadjuvant therapies targeting *BRAF* status in ATC and *RET* status in MTC, however, the efficacy of MKIs in the context of specific genetic driver mutations is less established. Although three patients had specific targetable mutations in our study (two patients had *RET*-mutated MTC, and one had $BRAF^{V600E}$ mutated PTC), lenvatinib was used instead of targeted therapy due to ease of compassionate access. In Australia, TKIs are typically reserved for patients with metastatic thyroid cancer or progressive disease, with selpercatinib only funded for MTC patients with disease recurrence after surgical management. As the results of several case series and clinical trials become available, increased access to selective RET inhibitors and BRAF / MEK inhibitors may allow refinement of neoadjuvant treatment pathways in Australia [47,48]. Until such time, our experience highlights real-world challenges in timely access to selective TKI and targeted therapies and presents neoadjuvant lenvatinib as a reasonable therapeutic alternative.

Our study is limited to five patients who received neoadjuvant lenvatinib for LATC. Due to this small sample size and heterogeneity of tumour histology in our series, we are unable to define predictive factors for response to lenvatinib treatment. Furthermore, although response to therapy was assessed using RECIST criteria, this does not capture changes in the profile of operative complexity and associated surgical morbidity. Currently there are no validated methodologies that assess change in surgical morbidity, however the MGH/MEEI-MSK-MD Anderson (MMM) and Invasive Thyroid Class score is being assessed in a current phase 2 clinical trial [49]. Additionally, the variability of adjuvant therapy administered prevents further analysis of long term durability of lenvatinib on locoregional control.

Lenvatinib demonstrates efficacy as neoadjuvant treatment for LATC, enabling safer surgical resection and minimising surgical morbidity. Further studies are needed to explore the ideal dose, duration and cessation period of neoadjuvant MKI therapies to optimise disease-free progression and overall survival.

CONCLUSION

Neoadjuvant multikinase inhibitor therapy demonstrates efficacy to facilitate surgery in LATC. The management approach and timing of surgery should be tailored to the individual patient's anatomy, tumour characteristics and therapeutic intent to enhance surgical outcomes and improve overall survival.

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