NTRK Fusion–Positive Thyroid Carcinoma: From Diagnosis to Targeted Therapy

Vicente R. Marczyk, MD, PhD[1]; Sasan Fazeli, MD[1]; Ramona Dadu, MD[1]; Naifa L. Busaidy, MD[1]; Priyanka Iyer, MD[1]; Mimi I. Hu, MD[1]; Steven I. Sherman, MD[1]; Sarah Hamidi, MD[1]; Sayed Mohsen Hosseini, MD, PhD[2]; Michelle D. Williams, MD[2]; Salmaan Ahmed, MD[3]; Mark J. Routbort, MD, PhD[4]; Raja Luthra, PhD[4]; Sinchita Roy-Chowdhuri, MD, PhD[2]; Francis Anthony San Lucas, PhD[5]; Keyur P. Patel, MD, PhD[4]; David S. Hong, MD[6]; Mark Zafereo, MD[7]; Jennifer R. Wang, MD, PhD[7]; Anastasios Maniakas, MD, PhD[7]; Steven G. Waguespack, MD[1]; and Maria E. Cabanillas, MD[1]

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ABSTRACT

PURPOSE Neurotrophic tropomyosin receptor kinase (*NTRK*) fusions may act as an oncogenic driver in thyroid carcinomas. Given their low frequency, clinical, pathological, and molecular data on these patients and their responses to targeted therapies are limited.

METHODS This is an observational retrospective study conducted at a single high-volume cancer center in the United States. Data were retrospectively collected from medical records.

RESULTS We included 65 patients (37 adult, 28 pediatric) with an *NTRK* fusion–positive thyroid carcinoma (24 *NTRK1*, 41 *NTRK3*), of which 54 were papillary thyroid carcinomas (PTC), four poorly differentiated thyroid carcinomas (PDTC), and seven anaplastic thyroid carcinomas (ATC). In PTC, an extensive follicular growth pattern was seen in 22 (41%) patients. In adults, *NTRK3* fusions were 3 times more frequent (nine *NTRK1*, 28 *NTRK3*), whereas in pediatric patients their frequencies were similar (15 *NTRK1*, 13 *NTRK3*; $P = .021$). In patients with PDTC/ATC treated with larotrectinib, we detected four emergent solvent front mutations (three *NTRK3* G623R, one *NTRK1* G595R) causing resistance to drug and disease progression. Three of them (two ATC, one PDTC) received second-line selitrectinib on a clinical trial. Partial responses were seen in all three patients, but both patients with ATC progressed within a year.

CONCLUSION *NTRK1/3* fusions are seen in PTC, PDTC, and ATC, and a follicular growth pattern was observed in a high proportion of cases. In patients treated with larotrectinib, *NTRK* solvent front mutations are the main resistance mechanism, frequently occurring in PDTC/ATC. Responses to single-agent TRK inhibitor are short-lived in patients with ATC; thus, these drugs should be used with caution in this population.

ACCOMPANYING CONTENT

Appendix

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INTRODUCTION

Most thyroid cancers arise from the thyroid follicular cells and are driven by genomic events, leading to the activation of the mitogen-activated protein kinase signaling pathway.[1,2] This activation usually occurs through mutations affecting *BRAF* and *RAS*, but can also occur through gene fusions involving *RET*, *NTRK*, *ALK*, and *BRAF*.[1,2] These driving events are generally mutually exclusive with a single oncogenic driver identified in most cases.[2]

The neurotrophic tropomyosin receptor kinase (*NTRK*) family comprises three genes (*NTRK1*, *NTRK2*, and *NTRK3*), which encode for three distinct TRK proteins (TRKA, TRKB, and TRKC, respectively).[3] The TRK proteins act as receptors for several neurotrophin ligands and are vital for the development and functioning of the nervous system.[3] In thyroid carcinomas, gene fusions primarily involve *NTRK1* and *NTRK3*.[4] The frequency of *NTRK* fusions ranges from 1% to 6% in adult papillary thyroid carcinomas (PTC)[2,5-17] and 4% to 26% in pediatric PTC,[18-26] making *NTRK* fusions the second most common fusion type after *RET* fusions in thyroid carcinomas.[2,11,14,18,25]

The identification of *NTRK* fusion–positive thyroid carcinomas has become of major importance given that two FDA-approved TRK inhibitors (larotrectinib and entrectinib) have demonstrated high rates of response in multiple cancer types.[27-30] For *NTRK* fusion–positive differentiated thyroid

CONTEXT

Key Objective

To examine the genetic, clinical, and pathological characteristics of *NTRK* fusion–positive thyroid cancer and the mechanisms of resistance to TRK inhibition.

Knowledge Generated

In this series of 65 patients, we show that *NTRK* fusions are mutually exclusive with other oncogenic drivers and primarily involve *NTRK1* and *NTRK3*, which may partner with more than 10 different genes. We also describe the first case series on the use of TRK-targeted agents in poorly differentiated thyroid carcinomas (PDTC)/anaplastic thyroid carcinomas (ATC) and document that solvent front mutations are the primary resistance mechanism in patients treated with first-generation TRK inhibitors.

Relevance

Identifying the most frequent *NTRK* fusion partners is crucial for designing and selecting appropriate next-generation sequencing panels, and our work serves as a guide for this. Moreover, our findings underscore the importance of tracking the emergence of solvent front mutations in patients with PDTC/ATC receiving first-line TRK inhibitors as well as the limitations of TRK-targeted therapies for ATC.

carcinomas, systemic treatment with larotrectinib or entrectinib resulted in an overall response rate of 86% and 54%, respectively.[27,31] Nonetheless, data on the use of TRK-targeted therapies for the treatment of poorly differentiated thyroid carcinomas (PDTC) and anaplastic thyroid carcinomas (ATC) remain limited and little is known about long-term outcomes and the mechanisms through which thyroid cancer cells may acquire resistance to TRK inhibition.[31]

Herein, we analyze the clinical, histological, and molecular data for a cohort of 65 patients diagnosed with an *NTRK* fusion–positive thyroid cancer seen at a high-volume cancer center in the United States. We report our experience with TRK-targeted therapies for patients diagnosed with PDTC and ATC, documenting *NTRK* emergent solvent front mutations as the main resistance mechanism to larotrectinib.

METHODS

Study Design

This is a retrospective study conducted at a single tertiary care cancer center in the United States. Patients seen at the University of Texas MD Anderson Cancer Center from June 2016 to June 2023 were eligible for inclusion. We included all patients who met the following criteria: (1) patient with a confirmed diagnosis of a follicular cell–derived thyroid carcinoma and (2) tumor confirmed to harbor an *NTRK1*, *NTRK2*, or *NTRK3* fusion. Pediatric patients were defined as patients age 18 years or younger at the time of diagnosis of thyroid cancer. The study was approved by the Institutional Review Board at the University of Texas MD Anderson Cancer Center under ID RC04-0933.

All *NTRK* fusions were detected through DNA- or RNA-based next-generation sequencing (NGS) assays performed in Clinical Laboratory Improvement Amendments–certified laboratories. A detailed description of which NGS panels were used is provided in the Results section. None of the fusions were detected using fluorescence in situ hybridization (FISH). For all patients, somatic molecular testing leading to the identification of the *NTRK* fusion was ordered by the patients' primary physician. Molecular testing is not universally performed at our institution for all patients diagnosed with thyroid carcinoma. Typically, these tests are ordered for patients with advanced or aggressive disease, for which systemic therapy would be considered.

Clinical, pathological, and molecular data were retrospectively collected from the medical records. Disease staging was reported at the initial diagnosis of thyroid cancer following the 8th edition of the American Joint Committee on Cancer staging system. Histopathological data were collected from the original pathology reports and included cancer type and subtype, predominant growth patterns, multifocality, extrathyroidal extension, and lymph node invasion.

Statistical Analysis

Descriptive statistics were calculated for demographic data. All analyses were conducted using R version 4.2. Continuous variables were reported as median and IQR and categorical variables were reported as absolute number and percentage. The association between categorical variables was tested using Fisher's exact test. The amount of missing data was reported for all variables.

RESULTS

Patient and Baseline Characteristics

We identified 65 patients, of which 28 (43%) were pediatric and 37 (57%) were adult patients (Table 1). Among

TABLE 1. Clinical Characteristics of *NTRK* Fusion–Positive Thyroid Carcinomas

Characteristic	All Patients (N = 65)	Pediatric (n = 28)	Adult (n = 37)
Age, years, median (IQR)	32.0 (15.0-54.0)	13.5 (9.75-16.0)	51.0 (37.0-62.0)
Sex, No. (%)			
Female	40 (61.5)	16 (57.1)	24 (64.9)
Male	25 (38.5)	12 (42.9)	13 (35.1)
Histology, No. (%)			
PTC	54 (83.1)	28 (100)	26 (70.3)
PDTC	4 (6.2)	0 (0)	4 (10.8)
ATC	7 (10.8)	0 (0)	7 (18.9)
Tumor size, cm, median (IQR)	4.5 (2.4-5.4)	4.8 (4.2-6.0)	3.4 (1.8-5.0)
T stage, No. (%)			
T1/T2	18 (32.7)	5 (17.9)	13 (48.1)
T3	22 (40.0)	15 (53.6)	7 (25.9)
T4	15 (27.3)	8 (28.6)	7 (25.9)
Missing	10	0	10
N stage, No. (%)			
N0	7 (12.1)	0 (0)	7 (23.3)
N1a	3 (5.2)	0 (0)	3 (10.0)
N1b	48 (82.8)	28 (100)	20 (66.7)
Missing	7	0	7
M stage, No. (%)			
M0	29 (46.8)	8 (28.6)	21 (61.8)
M1	33 (53.2)	20 (71.4)	13 (38.2)
Missing	3	0	3
Metastatic sites,[a] No. (%)			
Lung	30 (90.9)	20 (100.0)	10 (76.9)
Bone	9 (27.3)	3 (15.0)	6 (46.2)
Other[b]	5 (15.2)	2 (10.0)	3 (23.1)

Abbreviations: ATC, anaplastic thyroid carcinoma; PDTC, poorly differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma.
[a]Percentages were calculated considering only patients with metastatic (M1) disease. Percentages do not add to 100 since a single patient may have multiple metastatic sites.
[b]The other metastatic sites were brain (n = 3), liver (n = 2), kidney (n = 2), adrenal (n = 1), peritoneum (n = 1), and skeletal muscle (n = 1).

adults, the median age of diagnosis was 51.0 years (IQR, 37.0-62.0) and female patients represented 65% of cases. Among pediatric patients, the median age of diagnosis was 13.5 years (IQR, 9.8-16.0) and female patients represented 57% of cases (Table 1). The median time between the initial diagnosis of thyroid cancer and the detection of the *NTRK* fusion was 1.8 years (IQR, 0-5 years).

There were 54 (83%) PTC, 4 (6%) PDTC, and 7 (11%) ATC. Among pediatric patients, all 28 cancers were PTC at presentation. We did not observe any *NTRK* fusion–positive follicular thyroid carcinoma or oncocytic thyroid carcinoma. Interestingly, among the 54 patients with PTC, pathology reports described an extensive follicular growth pattern in 22 (41%) cancers, although only nine (17%) were diagnosed as a follicular variant of PTC. Focal areas of solid growth pattern were also noted in 9 (17%) of 54 PTC. Among evaluable PTC cases, 21 (48%) of 44 were multifocal and 31 (69%) of 45 had lymphovascular invasion.

As expected, our cohort was markedly enriched for advanced disease, with high frequencies of lymph node involvement, locally invasive disease, and distant metastases, as detailed in Table 1 and Figure 1. All 28 pediatric patients were N1b and 20 (71%) had distant metastases at diagnosis. In both pediatric and adult patients with M1 disease, lung was the most frequent metastatic site (30/33, 91%), followed by bone (11/33, 33%). Other less frequent metastatic sites included brain (n = 3), liver (n = 2), kidney (n = 2), adrenal (n = 1), peritoneum (n = 1), and skeletal muscle (n = 1), as shown in Figure 1. Distant metastatic disease in the absence of lung and bone metastases was not observed. Most patients (40/65, 62%) had already received initial therapy for thyroid cancer at the time of presentation to our institution and were referred to us for persistent, recurrent, and/or progressive disease.

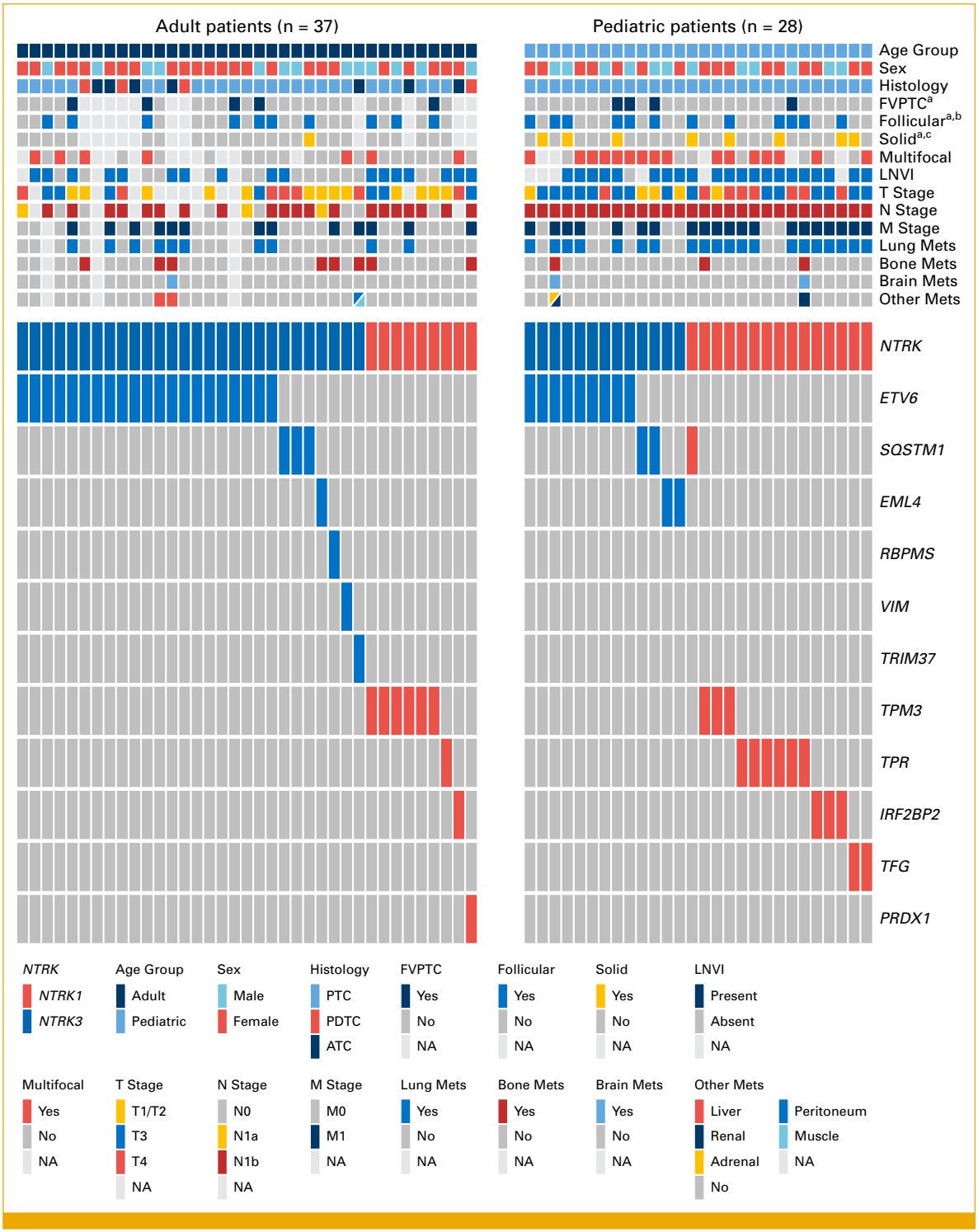

FIG 1. Oncoprint representation of clinical characteristics and *NTRK* fusions among 65 patients. Each column represents a single patient, and each row represents a single attribute. [a]These classifications are only applicable to PTC samples. [b]Follicular indicates an extensive or predominant follicular growth pattern, not necessarily meeting the diagnostic criteria for an FVPTC diagnosis. [c]Solid indicates focal areas of solid growth pattern, not necessarily meeting the diagnostic criteria for the solid subtype of PTC. ATC, anaplastic thyroid carcinoma; FVPTC, follicular variant of papillary thyroid carcinoma; LNVI, lymphovascular invasion; M, metastasis; mets, metastases; N, node; NA, not available; PDTC, poorly differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; T, tumor.

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NTRK Fusions in Pediatric and Adult Thyroid Carcinomas

Overall, fusions affecting *NTRK3* were more frequent than those affecting *NTRK1* (63% *v* 37%; Fig 1). No *NTRK2* fusions were found. The proportion between *NTRK1* and *NTRK3* fusions was significantly different for pediatric and adult patients (Fisher's exact $P = .021$). Among the 37 adult patients, *NTRK3* fusions accounted for 28 (76%) cases, whereas *NTRK1* fusions accounted for nine (24%) cases (Fig 1). Conversely, among the 28 pediatric patients, there were 15 (54%) *NTRK1* fusions and 13 (46%) *NTRK3* fusions (Fig 1).

All *NTRK* fusions were detected using DNA or RNA NGS. The most commonly used tests were MD Anderson Solid Tumor Genomic Assay RNA-Fusions version 2018 (23/65, 35%), FoundationOne (CDX or Heme; 10/65, 15%), Oncomine NGS (8/65, 12%), Caris RNA sequencing (5/65, 8%), Thyroseq (4/65, 6%), Afirma Xpression Atlas (3/65, 5%), Tempus xT (2/65, 3%), and NeoGenomics (2/65, 3%).

For *NTRK1*, we observed a total of six different fusion partners (*TPM3*, *TPR*, *IRF2BP2*, *TFG*, *SQSTM1*, and *PRDX1*; Fig 1), and the most common fusion partners were *TPM3* (9/24, 37%), followed by *TPR* (7/24, 29%) and *IRF2BP2* (4/24, 17%).

For *NTRK3*, there were six different fusion partners (*ETV6*, *EML4*, *SQSTM1, RBPMS*, *VIM*, and *TRIM37*), of which *ETV6* was the most common (30/41, 73%), followed by *SQSTM1* (5/41, 12%) and *EML4* (3/41, 7%; Fig 1). Only one fusion partner (*SQSTM1*) was observed partnering with both *NTRK1* and *NTRK3* (Fig 1), which is in accordance with previous reports.[5,10]

For 32 (49%) of 65 cases (eight *NTRK1* and 24 *NTRK3*), detailed information about which exons were fused together was available. All 24 *NTRK3* fusions involved exon 14, which was observed to partner with *ETV6*-exon4 (15/24, 62%), *ETV6*-exon5 (5/24, 21%), *SQSTM1*-exon5 (2/24, 8%), *EML4*-exon2 (1/24, 4%), and *RBPMS*-exon5 (1/24, 4%). Among the eight *NTRK1* fusions, most of them involved exon 10 (6/8, 75%), but fusions involving exon 9 (1/8, 12%) and exon 12 (1/8, 12%) were also observed. The fusion partners were *TPM3*-exon7 (5/8, 62%), *IRF2BP2*-exon1 (2/8, 25%), and *TPR*-exon21 (1/8, 12%).

In 64 (98%) of 65 cancers the *NTRK* fusion was the only oncogenic driver identified. In a single ATC case, we detected both a *BRAF* V600E mutation and an *NTRK3-TRIM37* fusion. The patient was treated with BRAF-targeted therapy on a clinical trial and was alive after 4 years of treatment. To our knowledge, this fusion has not been previously reported and it is unclear whether it is in fact oncogenic, given the clinical response to BRAF-targeted therapy. The novel fusion was detected by RNA sequencing at an outside laboratory and only the original report was available. We were unable to conduct studies to assess whether *NTRK* was expressed and whether the kinase domain was intact.

Clinical Differences Between *NTRK1* and *NTRK3* Fusion–Positive Thyroid Carcinomas

Next, we compared the clinical characteristics between *NTRK1* and *NTRK3* fusion–positive cancers. Among pediatric patients, we observed that *NTRK1* fusions were possibly associated with advanced tumor stage (Fisher's exact $P = .051$) but not M stage (Appendix Table A1). Among tumors classified as T4 (ie, tumors invading neck structures), seven (87%) of eight harbored *NTRK1* fusions and only one (12%) of eight harbored an *NTRK3* fusion. Conversely, among T1 and T2 cancers, only one (20%) of five harbored an *NTRK1* fusion (Appendix Table A1). Additionally, tumors harboring *NTRK1* fusions tended to be larger (5.3 cm *v* 4.5 cm, Mann-Whitney $P = .081$), although this difference did not reach statistical significance (Appendix Table A1). For adult patients, we did not observe differences between *NTRK1* and *NTRK3* fusion–positive tumors (Appendix Table A2).

Management of *NTRK* Fusion–Positive PDTC/ATC and the Emergence of Solvent Front Mutations

Among our 65 patients, 29 received first-line TRK-targeted therapy (28 larotrectinib, one entrectinib). Most of these patients (17/29, 59%) were treated on clinical trials and their outcomes have been previously reported (refer to Wagues-pack et al[31]), demonstrating durable responses in PTC cases. Hence, in the present study we focused specifically on the use of first- and second-line TRK-targeted therapies for PDTC and ATC, a scenario that has not been previously studied and merits attention. Seven cases with follow-up data were identified and are presented here in the form of a series of cases (Table 2, Figs 2 and 3), including two patients who received a TRK inhibitor for a PTC which later transformed into an ATC.

All seven patients received larotrectinib as first-line TRK inhibitor, and responses are detailed in Table 2 for each case. In four patients (two ATC, one PDTC, one PTC), we observed the emergence of *NTRK* mutations causing resistance to first-line agent and disease progression. In two patients, resistance mutations were detected using liquid biopsy, whereas only tissue NGS was performed for the other two. Three resistance mutations occurred in tumors harboring the *ETV6-NTRK3* fusion, all of which acquired the *NTRK3* G623R mutation. The fourth occurred in a tumor harboring the *IRF2BP2-NTRK1* fusion, which developed the *NTRK1* G595R mutation. Both the *NTRK3* G623R and *NTRK1* G595R mutations are known to act as solvent front mutations, meaning they are capable of hindering the binding of larotrectinib to the target protein, promoting resistance to the drug.[3,32] Nonetheless, both these mutations can be targeted with newer TRK inhibitors (selitrectinib,[33] repotrectinib,[34] and taletrectinib[35]).

Three patients harboring solvent front mutations received second-line treatment with selitrectinib on a clinical trial. All three (100%) had a partial response, with disease volume

TABLE 2. Cases Series of Patients Diagnosed With PDTC or ATC Receiving TRK-Targeted Therapy

ID	Baseline and Primary Treatment	First-Line TRK Inhibitor	Second-Line TRK Inhibitor
1	Age at diagnosis/sex: Female, 57 years Diagnosis: stage IVB ATC Primary treatment: surgery + chemoRT Progression: new lung metastases after 5 months Somatic alterations *IRF2BP2-NTRK1* fusion	Larotrectinib on trial Best response: PR (−50%) after cycle 4 Progression (new metastases) after cycle 6 Somatic alterations at progression *IRF2BP2-NTRK1* fusion *NTRK1* G595R mutation *CDKN2A/CDKN2B* loss	Selitrectinib on trial Best response: PR (-48%) after cycle 6 Progression (peritoneal carcinomatosis) after cycle 7 Somatic alterations at progression unknown (not rebiopsied)
2	Age at diagnosis/sex: Female, 62 years Diagnosis: stage IVB ATC; Pan-TRK immunohistochemistry on the resected tumor had positive cytoplasmic expression in approximately 20% of tumor cells (Fig 2) Somatic alterations *ETV6-NTRK3* fusion *TP53* mutation Primary treatment: chemoRT (60 Gy + carboplatin-paclitaxel) Progression: new lung metastases after 5 months	Larotrectinib on trial Evaluable but nonmeasurable disease at enrollment (small FDG-avid lung nodules) Response to therapy: After two cycles, lung nodules decreased in size but there were new FDG-avid nodes (portacaval and iliac), thought to represent progression. Patient kept on trial. Lymph nodes were not biopsied and resolved after cycle 6. Patient on larotrectinib for more than 5 years, with no significant changes in her lung nodules. In retrospect, the lung metastases may represent PTC	Not applicable
3	Age at diagnosis/sex: Female, 9 years Diagnosis: PTC (confirmed ATC transformation during TRK-targeted therapy) Primary treatment: surgery + RAI Progression: Patient lost follow-up and returned at age 29 years with metastatic PTC Somatic alterations (metastatic PTC) *ETV6-NTRK3* fusion *SPEN* mutation	Larotrectinib (standard of care) Response: PR until cycle 19, when patient experienced oligoprogression at mediastinal lymph node. Biopsy revealed PTC harboring *NTRK3* G623R mutation. Decision was to surgically excise the progressing lymph nodes and continue larotrectinib. After 6 months, new oligoprogression in the jaw. Mandibulectomy performed, revealing ATC transformation (Fig 3). Molecular testing unsuccessful. Patient kept on larotrectinib. Recently, patient developed several new metastatic sites, for which second-line therapy will be pursued	Not applicable
4	Age at diagnosis/sex: Male, 63 years Diagnosis: suspected stage IVb ATC. Rapidly growing indurated neck mass causing hoarseness and dyspnea. Biopsy consistent with PTC, but clinical picture suggestive of ATC. Somatic alterations *NTRK3-SQSTM1* fusion *RB1* and *CENPE* mutations	Neoadjuvant larotrectinib Although the patient did not have distant metastases, neck disease was considered inoperable; hence, neoadjuvant therapy was recommended. During cycle 1, he had radiographic and clinical progression, with tumor breaking through the skin. Pembrolizumab was added. After single dose of pembrolizumab, he developed grade 4 immune-mediated cholangiohepatitis; hence, drug was stopped. Partial response noted after 2 months and sustained after 5 months, allowing surgical resection. Surgical pathology showed an 8.5-cm tumor area, of which 95% were nonviable necrotic cells with extensive inflammatory infiltrate	Not applicable
5	Age at diagnosis/sex: Female, 38 years Diagnosis: PTC (likely ATC transformation during TRK-targeted therapy) Primary treatment: surgery + RAI Progression: 14 years after initial diagnosis patient developed RAI-refractory disease Somatic alterations (at progression) *ETV6-NTRK3* fusion *TP53* mutation	Larotrectinib on trial Best response: PR Trial at an outside institution, hence detailed follow-up data unavailable Progressed after cycle 14 (pleural nodule and osteolytic spinal metastases). Progressive site biopsied outside, but we did not receive the slides for review or molecular testing. Referred to us for selitrectinib trial	Selitrectinib on trial Best response: PR (−31%) after cycle 2 Progression after cycle 10 (cerebellar metastasis and pleural metastases). She declined biopsy of progressive sites, hence only liquid biopsy collected at progression Somatic alterations at progression (liquid biopsy) *NTRK3* G623R mutation *TP53*, *TERTp*, *NF1*, *BRCA2*, and *EGFR* mutations likely ATC transformation

(continued on following page)

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TABLE 2. Cases Series of Patients Diagnosed With PDTC or ATC Receiving TRK-Targeted Therapy (continued)

ID	Baseline and Primary Treatment	First-Line TRK Inhibitor	Second-Line TRK Inhibitor
6	Age at diagnosis/sex: Male, 27 years Diagnosis: PTC → PDTC transformation Primary treatment: surgery + RAI Progression: 4 years after initial diagnosis patient referred to us for progressive RAI-refractory disease in the neck and lungs. Neck progression confirmed to be PDTC transformation Somatic alterations (at progression) *ETV6-NTRK3* fusion *TP53* and *TERTp* mutations	Larotrectinib on trial Best response: PR (−92%) after cycle 20 Progression after cycle 52 (lung metastases) Somatic alterations at progression *NTRK3* G623R mutation *ETV6-NTRK3* fusion *TP53* and *TERTp* mutations *The *NTRK3* solvent front mutation was also identified by a liquid biopsy This case has been previously reported by Waguespack et al[31]	Selitrectinib on trial Best response: PR (−63%) after cycle 26 Patient currently on cycle 38 with evidence of oligoprogression
7	Age at diagnosis/sex: Female, 64 years Diagnosis: PDTC Primary treatment: surgery + RAI Progression: After 1 year, progression in the neck and bones. Initially managed with external beam radiation Somatic alterations (at progression) *ETV6-NTRK3* fusion	Larotrectinib on trial Best response: PR (−70%) after 19 cycles Patient experienced disease progression during a drug hold for pneumonia and died 3 months later. Her disease was not biopsied at progression, so we do not know whether the molecular mechanism of her progression. This case has been previously reported by Waguespack et al[31]	Not applicable

Abbreviations: ATC, anaplastic thyroid carcinoma; ID, patient identification; PDTC, poorly differentiated thyroid carcinoma; PTC, papillary thyroid carcinoma; PR, partial response; RAI, radioactive iodine.

reductions ranging from 31% to 63%. Unfortunately, all three patients experienced disease progression. In two patients with ATC (patients 1 and 5), disease progression and patient death occurred within a year. The third patient (patient 6) had PDTC and progressed after 26 cycles. He was kept on the drug after progression and was still alive on cycle 38 of selitrectinib at data cutoff.

DISCUSSION

Our single-center study reports the largest series to date on *NTRK* fusion–positive thyroid carcinomas, characterizing the clinical and histological aspects of the disease, as well as the most frequent *NTRK* fusions encountered in adult and pediatric patients with advanced disease. We report the first case series on the use of TRK-targeted therapies in PDTC/ATC and document that acquired solvent front mutations affecting *NTRK1* and *NTRK3* are the main mechanism leading to first-line TRK-targeted therapy resistance.

Previous studies have investigated *NTRK* fusion–positive thyroid carcinomas, as recently reviewed by Haddad et al.[4] In accordance with the previous reports, we observed that thyroid carcinomas driven by *NTRK* fusions have some histopathological particularities that may raise suspicion for this particular driver.[10] Although most of these tumors do have the nuclear features of PTC, they usually exhibit a predominant follicular growth pattern, which may be mixed with papillary and micropapillary structures.[5,10,19,26] They may also demonstrate diffuse sclerosis and areas of solid growth pattern in some cases.[10,19,26]

In our study, we observed a similar frequency of *NTRK1* and *NTRK3* fusions among pediatric thyroid carcinomas (15 *NTRK1*, 13 *NTRK3*). Contrary to these findings, Ricarte-Filho et al[19] studied a US pediatric population and reported that *NTRK3* fusions were 2 times more frequent (13 *NTRK3*, 7 *NTRK1*). Likewise, Pekova et al[18] studied pediatric patients from the Czech Republic and observed that *NTRK3* fusions were 5 times more common among pediatric patients (14 *NTRK3*, three *NTRK1*). Similar to our results, Lee et al[20] studied a pediatric population from South Korea and observed the same frequency for both fusions (two *NTRK1*, two *NTRK3*), but their small number of cases limits conclusions. Although the reason for these differences remains unclear, one possible explanation is that our pediatric population was strongly biased toward patients with more advanced disease. Other possible explanations include populational variations and differences between the fusion assays used in each study.

Previous research including various cancer types reported that solvent front mutations are the most common resistance mechanism to first-generation TRK-targeted agents.[3,36] In the larotrectinib trial, the investigators detected 11 cases of kinase domain resistance mutations, which could be classified into three types: seven solvent front (five *NTRK1* G595R, two *NTRK3* G623R), two gatekeeper (two *NTRK1* F589L), and two xDFG mutations (one *NTRK1* G667S, one *NTRK3* G696A; xDFG mutations refer to the amino acid preceding the activation loop DFG motif).[29] In a different study analyzing 15 cases of acquired resistance to larotrectinib or entrectinib, solvent front mutations represented 87% (13 out of 15) of the cases (seven *NTRK3* G623R, four *NTRK1* G595R, one *NTRK2* G639L, and one *NTRK3* G623E).[37] To our knowledge, our study is the first series focused on patients with thyroid cancer, showing that thyroid cancer cells can be resistant to TRK-targeted therapy by the same mechanism: solvent front mutations, most specifically *NTRK3* G623R and *NTRK1* G595R. Interestingly, we managed to detect these mutations using liquid biopsy in the two cases

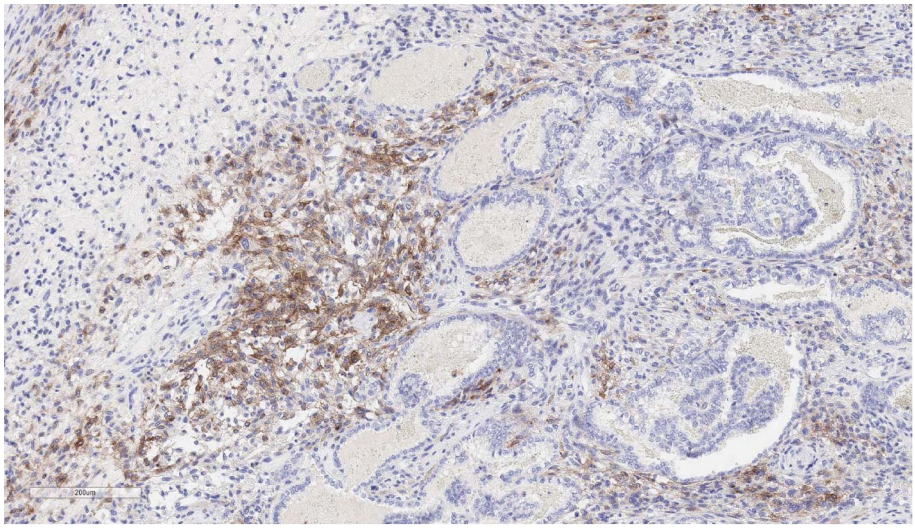

FIG 2. Pathology on resected primary anaplastic thyroid cancer. The anaplastic component shows spindled morphology and is positive for pan-TRK by immunohistochemistry.

submitted for liquid biopsy, suggesting it may be a valuable tool to monitor the emergence of such mutations.

Data on the use of TRK-targeted agents for the treatment of PDTC and ATC are very limited.[4] *Waguespack et al* reported that the response rates for ATC are much lower than those observed in PTC (29% *v* 86%, respectively).[31] Our small experience using TRK-targeted agents to treat *NTRK* fusion–positive ATC and PDTC builds upon that knowledge by describing results with second-generation agents, which can theoretically target both solvent front mutations (*NTRK3* G623R and *NTRK1* G595R).[3,36] Our experience is limited to selitrectinib,[33] a drug that is no longer being developed. Repotrectinib[34,38,39] and taletrectinib[40,41] are, however, next-generation TRK and ROS1 inhibitors that merit being studied in patients with thyroid cancer who have progressed on a first-generation TRK inhibitor. Unfortunately, as shown for patient 1 and patient 5, targeting solvent front mutations with a single agent was not sufficient to achieve durable responses in ATC in our case series, suggesting that TRK-targeted drugs as monotherapy may not be the optimal regimen for patients with ATC. Additional studies will need to test whether combining these agents with other drugs is safe and would yield more durable responses.[32] As for the

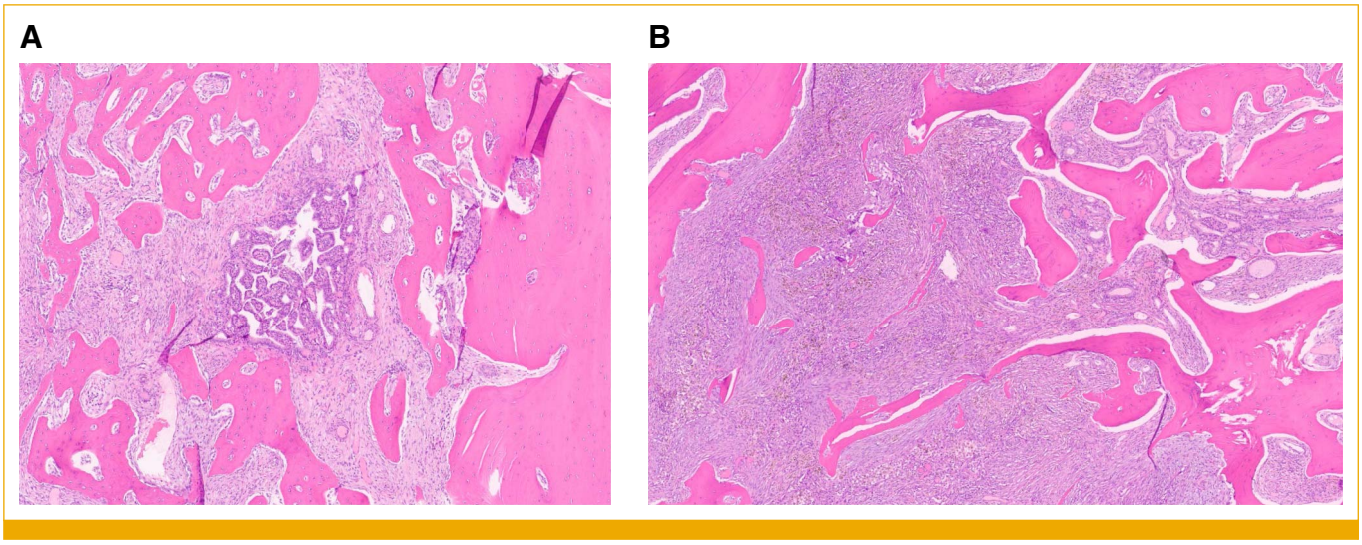

FIG 3. Hematoxylin and eosin–stained histologic sections showing (A) metastatic papillary thyroid carcinoma retaining papillary architecture and (B) more cellular spindled component consistent with anaplastic transformation within mandibular bone.

treatment of PDTC, our two patients responded to larotrectinib much longer (patients 6 and 7 in Table 2), although both still ultimately experienced disease progression. Although very limited, our experience with TRK-targeted drugs for PDTC indicates that those drugs may be a good option of systemic therapy, but close follow-up is advisable.

In accordance with previous studies, we observed that *NTRK* fusions are mutually exclusive with other oncogenic drivers.[2] Hence, it is reasonable to use a stepwise testing approach, as recently proposed.[4,2] NGS is the gold standard approach to search for oncogenic drivers, as NGS panels can test for several drivers simultaneously with very high accuracy.[4,2] Notably, the identification of *NTRK* fusions can be very challenging from a technical point of view, even for NGS panels.[13] DNA-based NGS panels may be used to detect the most frequent fusions (eg, *ETV6-NTRK3*). However, if novel fusions are encountered or if no oncogenic driver can be identified by DNA-based NGS, RNA-based NGS is mandatory.[13] The detection of *NTRK* fusions through immunohistochemistry or FISH is not the preferred test in thyroid cancers, given their low frequency (ie, low pretest probability) and the variable performance of such assays, but it may be considered in low-resource settings or when tissue is insufficient for RNA sequencing.[4]

Our study has some limitations. Our population was strongly biased toward patients with aggressive disease. Moreover, the retrospective and observational nature of our clinical data poses an additional limitation to interpretation, given the high propensity to selection biases. Additionally, a pathology review of each case was not possible, and data were retrieved from pathology reports. However, taken together that most patients with thyroid cancer do not need systemic treatment and the low frequency of *NTRK* fusions in this cancer type, observational studies still offer a significant contribution to our understanding of the disease. For *NTRK* fusion–positive ATC, which is even more rare, small case series are likely to be the main source of evidence to guide treatment.

Overall, our study offers a comprehensive characterization of the clinical, histological, and molecular aspects of *NTRK* fusion–positive thyroid carcinomas. Given that TRK-targeted therapies are now available, clinicians should be familiar with this specific disease subtype and how to properly diagnose those patients, so they can be offered the best available treatment options.

AFFILIATIONS

[1]Department of Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer, Houston, TX
[2]Department of Pathology, The University of Texas MD Anderson Cancer, Houston, TX
[3]Department of Neuroradiology, The University of Texas MD Anderson Cancer, Houston, TX
[4]Department of Hematopathology, The University of Texas MD Anderson Cancer, Houston, TX
[5]Clinical Bioinformatics, The University of Texas MD Anderson Cancer, Houston, TX
[6]Department of Investigational Cancer Therapeutics, The University of Texas MD Anderson Cancer, Houston, TX
[7]Department of Head & Neck Surgery, The University of Texas MD Anderson Cancer, Houston, TX

CORRESPONDING AUTHOR

Maria E. Cabanillas, MD; e-mail: mcabani@mdanderson.org.

EQUAL CONTRIBUTION

V.R.M. and S.F. contributed equally to this work as co-first authors.
S.G.W. and M.E.C. contributed equally to this work as co-senior authors.

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AUTHOR CONTRIBUTIONS

Conception and design: Vicente R. Marczyk, Sasan Fazeli, Priyanka Iyer, Mimi I. Hu, Steven I. Sherman, David S. Hong, Mark Zafereo, Jennifer R. Wang, Maria E. Cabanillas
Provision of study materials or patients: Naifa L. Busaidy, Mimi I. Hu, Steven I. Sherman, Raja Luthra, Sinchita Roy-Chowdhuri, Keyur P. Patel, David S. Hong, Mark Zafereo, Jennifer R. Wang, Anastasios Maniakas, Steven G. Waguespack, Maria E. Cabanillas
Collection and assembly of data: Vicente R. Marczyk, Sasan Fazeli, Sayed Mohsen Hosseini, Mark J. Routbort, Raja Luthra, Francis Anthony San Lucas, Keyur P. Patel, David S. Hong, Maria E. Cabanillas
Data analysis and interpretation: Vicente R. Marczyk, Sasan Fazeli, Ramona Dadu, Naifa L. Busaidy, Mimi I. Hu, Steven I. Sherman, Sarah Hamidi, Sayed Mohsen Hosseini, Michelle D. Williams, Salmaan Ahmed, Sinchita Roy-Chowdhuri, Keyur P. Patel, David S. Hong, Anastasios Maniakas, Steven G. Waguespack, Maria E. Cabanillas
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

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Ramona Dadu
Honoraria: Bayer
Consulting or Advisory Role: Exelixis
Research Funding: AstraZeneca (Inst), Merck (Inst), Eisai (Inst), Exelixis (Inst)

Naifa L. Busaidy
Honoraria: Eisai, Exelixis, Lilly
Consulting or Advisory Role: Eisai

Priyanka Iyer
Research Funding: Bristol Myers Squibb

Mimi I. Hu
Employment: crispr therapeutics
Research Funding: Lilly
Other Relationship: Lilly

Steven I. Sherman
Employment: Southwest OB/GYN Associates, Methodist Hospital
Honoraria: Novartis, Crinetics Pharmaceuticals

Michelle D. Williams
Speakers' Bureau: Springer
Research Funding: Bayer Health

Keyur P. Patel
Consulting or Advisory Role: Astellas Pharma, Astellas Pharma, Syros Pharmaceuticals

David S. Hong
Employment: MD Anderson Cancer Center
Stock and Other Ownership Interests: OncoResponse, Telperian, MolecularMatch, crossbridge Bio
Consulting or Advisory Role: Bayer, Amgen, Janssen, BeiGene, Bristol Myers Squibb Company, Mirati Therapeutics, Sanofi and Genzyme US Companies
Research Funding: Genentech (Inst), Amgen (Inst), Abbvie (Inst), Bayer (Inst), Pfizer (Inst), Novartis (Inst), Mirati Therapeutics (Inst), Bristol Myers Squibb (Inst), Incyte (Inst), Deciphera Pharmaceuticals Inc (Inst), Merck Sharp & Dohme LLC (Inst)
Travel, Accommodations, Expenses: Genmab, Society for Immunotherapy of Cancer, Bayer Schering Pharma, ASCO, AACR, Telperian, CLCC

Mark Zafereo
Research Funding: Merck (Inst), Lilly (Inst)
Other Relationship: American Academy of Otolaryngology-Head and Neck Surgery
Uncompensated Relationships: International Thyroid Oncology Group
Open Payments Link: https://openpaymentsdata.cms.gov/physician/923970

Anastasios Maniakas
Research Funding: Jazz Pharmaceuticals
Other Relationship: Thryv Therapeutics Inc

Steven G. Waguespack
Honoraria: Bayer
Consulting or Advisory Role: Bayer, Camurus
Travel, Accommodations, Expenses: Bayer

Maria E. Cabanillas
Honoraria: Boston University, University of Miami
Consulting or Advisory Role: Bayer, Exelixis, Novartis, Thryv
Research Funding: Eisai, Roche/Genentech, Exelixis, Merck

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APPENDIX

TABLE A1. Clinical Differences Between *NTRK1* and *NTRK3* Fusion–Positive Papillary Thyroid Carcinoma in Pediatric Patients

Patient/Tumor Characteristic	*NTRK1* (n = 15)	*NTRK3* (n = 13)	*P*
Age, years, median (IQR)	15.0 (10.0-16.0)	13.0 (10.0-16.0)	1
Sex, No. (%)			
Female	9 (60.0)	7 (53.8)	1
Male	6 (40.0)	6 (46.2)	
Size, cm, median (IQR)	5.3 (4.8-6.7)	4.5 (3.4-5.6)	.081
Multifocal, No. (%)			
Yes	7 (58.3)	9 (81.8)	.37
No	5 (41.7)	2 (18.2)	
Missing	3	2	
Lymphovascular invasion, No. (%)			
Yes	13 (100)	8 (88.9)	.41
No	0 (0)	1 (11.1)	
Missing	2	4	
T stage, No. (%)			
T1/T2	1 (6.7)	4 (30.8)	.051
T3	7 (46.7)	8 (61.5)	
T4	7 (46.7)	1 (7.7)	
N Stage, No. (%)			
N0/N1a	0 (0)	0 (0)	1
N1b	15 (100)	13 (100)	
M stage, No. (%)			
M0	2 (13.3)	6 (46.2)	.096
M1	13 (86.7)	7 (53.8)	

TABLE A2. Clinical Differences Between *NTRK1* and *NTRK3* Fusion–Positive Papillary Thyroid Carcinoma in Adult Patients

Patient/Tumor Characteristic	*NTRK1* (n = 6)	*NTRK3* (n = 20)	*P*
Age, years, median (IQR)	39.0 (36.5-46.8)	48.0 (35.5-55.0)	.48
Sex, No. (%)			
Female	3 (50.0)	13 (65.0)	.64
Male	3 (50.0)	7 (35.0)	
Size, cm, median (IQR)	2.6 (1.6-3.8)	2.7 (1.8-4.1)	.53
Multifocal, No. (%)			
Yes	1 (16.7)	4 (26.7)	1
No	5 (83.3)	11 (73.3)	
Missing	0	5	
Lymphovascular invasion, No. (%)			
Yes	4 (66.7)	6 (35.3)	.34
No	2 (33.3)	11 (64.7)	
Missing	0	3	
T stage, No. (%)			
T1/T2	4 (66.7)	8 (53.3)	.53
T3	2 (33.3)	3 (20.0)	
T4	0	4 (26.7)	
Missing	0	5	
N stage, No. (%)			
N0	1 (16.7)	4 (23.5)	.80
N1a	0 (0)	3 (17.6)	
N1b	5 (83.3)	10 (58.8)	
Missing	0	3	
M stage, No. (%)			
M0	5 (83.3)	13 (72.2)	1
M1	1 (16.7)	5 (27.8)	
Missing	0	2	

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