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Targeted Oncogene Therapy Before Surgery in Pediatric Patients With Advanced Invasive Thyroid Cancer at Initial Presentation
Is It Time for a Paradigm Shift?

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IMPORTANCE Initial data suggest the effectiveness of oncogene-specific targeted therapies in inducing tumor regression of diverse cancers in children and adults, with minimal adverse effects.

OBSERVATIONS In this review, preliminary data suggest that systemic therapy may be effective in inducing tumor regression in pediatric patients with unresectable invasive thyroid cancer. Although most pediatric patients with thyroid cancer initially present with operable disease, some children have extensive disease that poses substantial surgical challenges and exposes them to higher than usual risk of operative complications. Extensive disease includes thyroid cancer that invades the trachea or esophagus or encases vascular or neural structures. Previous efforts to manage extensive thyroid cancer focused on surgery with near-curative intent. With the recent development of oncogene-specific targeted therapies that are effective in inducing tumor regression, with minimal drug-associated adverse effects, there is an opportunity to consider incorporating these agents as neoadjuvant therapy. In patients with morbidly invasive regional metastasis or with hypoxia associated with extensive pulmonary metastasis, neoadjuvant therapy can be incorporated to induce tumor regression before surgery and radioactive iodine therapy. For patients with widely invasive medullary thyroid cancer, in whom the risk of surgical complications is high and the likelihood of surgical remission is low, these agents may replace surgery depending on the response to therapy and long-term tolerance.

CONCLUSIONS AND RELEVANCE With oncogene-specific targeted therapy that is associated with substantial tumor regression and low risk of adverse reactions, there appears to be an opportunity to include children with advanced invasive thyroid cancer in clinical trials exploring neoadjuvant targeted oncogene therapy before or instead of surgery.

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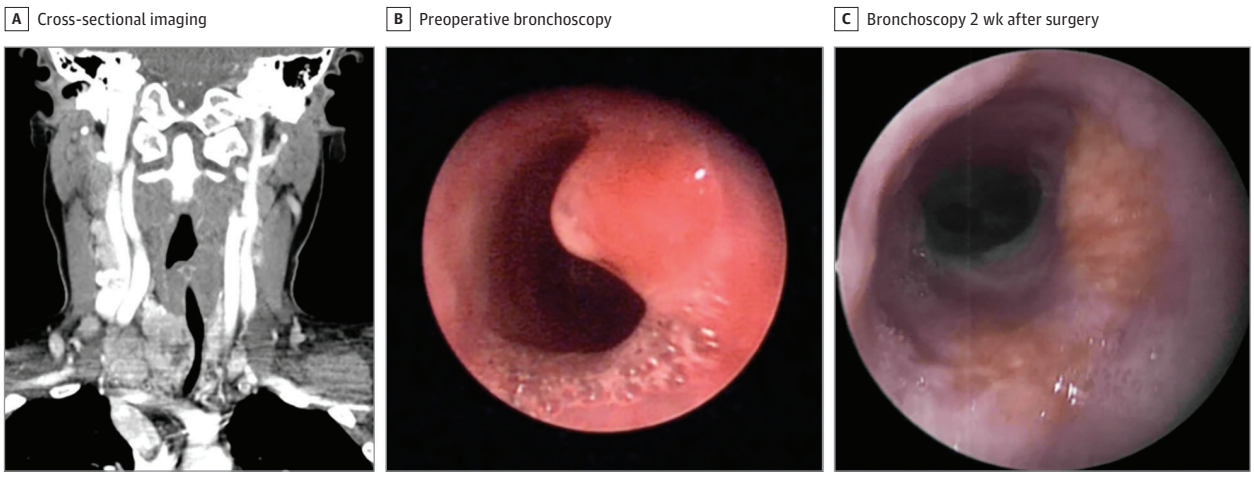
Surgery is the initial treatment for most pediatric patients with thyroid cancer.[1] In the setting of differentiated thyroid cancer (DTC), surgical resection is often followed by radioactive iodine (RAI) therapy. In patients who develop recurrent disease or pulmonary metastasis, RAI dosing may be repeated, although the probability of achieving remission is reduced. In addition, RAI therapy is ineffective in treating patients with poorly DTC (PDTC) or medullary thyroid cancer (MTC).[2]

Adult patients with refractory anatomically progressive thyroid cancer may be offered systemic therapy with multitargeted kinase inhibitors (MKIs). Most patients treated with MKIs have only a partial response to therapy, and the clinical benefits are often transient.[3] Within the last 2 years, a number of selective oncogene-specific targeted inhibitors have been investigated in clinical trials for patients with RAI-refractory DTC and advanced MTC. These agents, including rearranged during transfection (RET) inhibitors (pralsetinib/BLU-667 and selpercatinib/LOXO-292), tropomyosin receptor kinase (TRK) inhibitors (larotrectinib), and anaplastic lymphoma kinase (ALK) inhibitors (ensartinib and alectinib), have shown effectiveness in inducing tumor regression with substantially fewer adverse effects compared with MKIs.[3-6]

Within the field of pediatrics, case reports have described the use of MKIs in children with papillary thyroid carcinoma.[7,8] However, there is no consensus on the definition of refractory disease or for selecting patients who might benefit from MKIs or oncogene-specific targeted agents.

Initial data[5,6] suggest the effectiveness of oncogene-specific targeted therapies in inducing tumor regression of diverse cancers in children and adults, with minimal adverse effects. Therefore, we propose a paradigm shift in the approach to treatment of select pediatric patients who initially present with widely invasive thyroid cancer, in whom neoadjuvant therapy with MKIs or oncogene-specific targeted therapy may be beneficial before a surgical procedure in an effort to reduce surgical morbidity.

Figure 1. Nine-Year-Old Patient With Invasive Papillary Thyroid Cancer (Case 1)



A, Cross-sectional imaging of a large right thyroid mass with tracheal narrowing and extensive bilateral cervical lymphadenopathy. B and C, Bronchoscopy showing intramural involvement of the trachea by tumor (B), with follow-up bronchoscopy 2 weeks after surgery showing routine healing, with normal airway caliber (C).

Observations

In this review, preliminary data suggest that systemic therapy may be effective in inducing tumor regression in pediatric patients with unresectable invasive thyroid cancer. Although most pediatric patients with thyroid cancer initially present with operable disease, some children have extensive disease that poses substantial surgical challenges and exposes them to higher than usual risk of operative complications. Extensive disease includes thyroid cancer that invades the trachea or esophagus or encases vascular or neural structures.

The following 2 case reports highlight the clinical presentation of children and adolescents with advanced invasive thyroid cancer at initial presentation. In these 2 patients, the paradigm shift proposed above could have been incorporated into patient care in case 1 and was incorporated into patient care in case 2.

Case 1

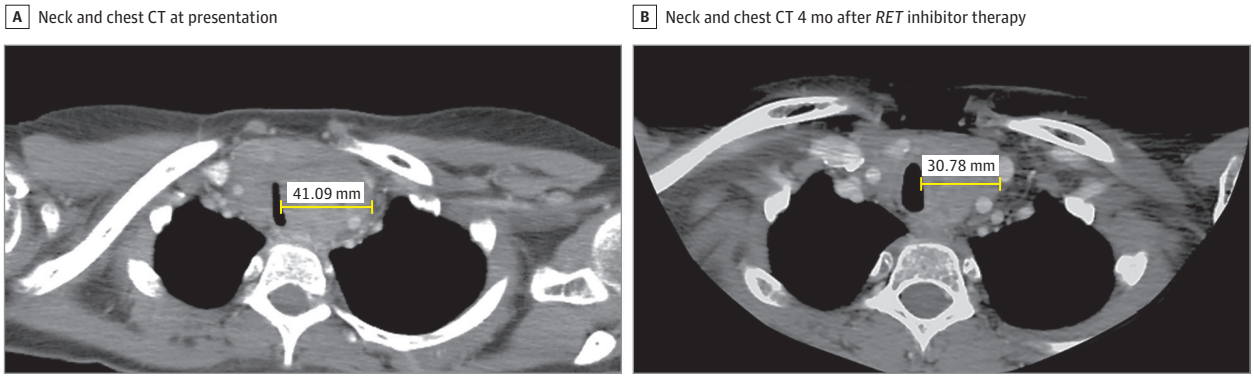
A 9-year-old boy was seen at the emergency department with a 1-month history of worsening asthma and an enlarging neck mass that had failed to respond to antibiotic therapy. Tracheal deviation was noted on radiography, and cross-sectional imaging showed a large right thyroid mass with tracheal narrowing to a diameter of 3 mm as well as extensive bilateral cervical lymphadenopathy in levels II to IV and VI (**Figure 1**A). Fine-needle aspiration confirmed the suspected diagnosis of papillary thyroid cancer (PTC). The patient underwent direct laryngoscopy and bronchoscopy before intubation for surgery, which showed intramural extraluminal tumor involvement of the trachea. Primary surgical therapy included total thyroidectomy, therapeutic bilateral level VI dissection, and bilateral modified radical neck dissection of levels II to IV. The right recurrent laryngeal nerve was electively sacrificed because of complete encasement of the nerve by a large mass of tumor adherent to the airway.

Pathological examination confirmed solid-variant PTC with extensive lymphovascular and extrathyroidal invasion. Follow-up bronchoscopy with injection laryngoplasty was performed 3 weeks later and showed no improvement in airway caliber after tumor resection. Repeated imaging confirmed intramural involvement of the trachea by tumor and no residual thyroid tissue in the cervical bed (Figure 1B). Tracheal resection with end-to-end reanastomosis was performed, with 3.5 cm of tracheal tissue removed. Gross intraluminal tumor was removed at the time of surgery, and margins were microscopically positive. Follow-up bronchoscopy at 1 week and 2 weeks after surgery showed routine healing, with normal airway caliber (Figure 1C). The patient was treated with 139 mCi of I^{131}, with final TNM classification of pT4aN1bM1 secondary to a solitary macronodular pulmonary lesion noted on post-I^{131} therapy whole-body scan. At 22 months after surgery, the patient is asymptomatic but with permanent hypoparathyroidism and persistent pulmonary PTC.

Case 2

An 18-year-old girl presented with a visible neck mass that had increased in size over the preceding 4 months, accompanied by recent onset of stridor when supine (requiring the head to be raised to sleep), dyspnea on exertion during routine daily activities (eg, climbing stairs), and intermittent episodes of facial flushing. Neck and chest computed tomography revealed a large tumor extending from the thyroid into the mediastinum, tracheal narrowing to 85% (**Figure 2**A), and encasement of the great vessels. Fine-needle aspiration was performed and confirmed MTC. No other family members had a history of MTC or multiple endocrine neoplasia type 2 tumors. Somatic and germline testing revealed a somatic *RET* (OMIM 164761) proto-oncogene alteration in codon 918 (Met918Thr). After consultation with the head and neck surgeon, the endocrine surgery service, the thoracic surgical team, the thyroid oncologist, and the patient and her family, it was decided that the patient would be enrolled in a phase 1/2 study[9] using a selective RET inhibitor rather than pursuing a procedure with a high risk of surgical morbidity and even mortality with a low likelihood of surgical remission. Within 4 months of initiation of pralsetinib, the tumor was smaller on examination, and the patient's airway and flush-

Figure 2. Eighteen-Year-Old Patient With Invasive Medullary Thyroid Cancer (Case 2)



CT indicates computed tomography; RET, rearranged during transfection.

ing symptoms had resolved, with 25% regression in size noted on repeated neck and chest computed tomography (Figure 2B). The patient will continue receiving pralsetinib, with no plans for attempted surgical resection.

Discussion

Within the last 5 to 10 years, increasing numbers of MKIs have been incorporated into clinical practice for adult patients with RAI-refractory DTC with anatomical progression or widely metastatic MTC.[3] In the field of pediatrics, case reports have been described in which MKIs have been used[7,8]; however, the data are limited, and there is no consensus on when to initiate therapy or which oral chemotherapeutic agent should be used. First-generation kinase inhibitors used to treat RAI-refractory DTC and metastatic MTC have in common the targeting of vascular endothelial growth factor receptor (VEGFR), among other kinases, and thus have substantial adverse effects in adults.[3] The identification of oncogene-specific targeted therapies with improved effectiveness for tumor regression and fewer adverse effects and reactions[3] may provide opportunities to treat pediatric patients who have anatomically progressive disease for which traditional therapy (surgery with or without RAI therapy for DTC and surgery for MTC) has been shown to be ineffective. These novel oncogene-specific targeted therapies also provide an opportunity for a paradigm shift in the treatment of patients who initially present with widely invasive disease at diagnosis, in whom surgery involves higher than usual risk of surgical morbidity. For these patients, the use of neoadjuvant chemotherapy that is administered as a first step to reduce tumor burden may optimize outcomes and reduce treatment-associated complications.

The following 4 MKIs have received US Food and Drug Administration approval for the treatment of advanced thyroid cancer: sorafenib and lenvatinib mesylate for DTC and cabozantinib and vandetanib for MTC.[3] In clinical trials among adults,[3] MKIs have induced tumor regression; however, the response to therapy is often transient, with continued progression of tumor growth 10 to 30 months after initiation of therapy.[3,10] In addition, up to 76% of patients with advanced thyroid carcinoma develop adverse effects associated with therapy, including fatigue, weight loss, hypertension, dermatitis, QT interval prolongation (with vandetanib use), and gastrointestinal ulcers and hemorrhage (bleeding from the ulcer) (with cabozantinib use).[3] Multitargeted kinase inhibitors may be considered as first-line agents for neoadjuvant therapy in pediatric patients with metastatic RAI-refractory DTC and in pediatric patients with metastatic MTC. In addition, MKIs may be used for neoadjuvant therapy in patients without a targetable oncogene; however, in tumors that harbor a targetable driver alteration, the use of newer oncogene-specific targeted agents (**Table 1**[9,11-18] and **Figure 3**) may be associated with earlier and more rapid regression of tumor size.

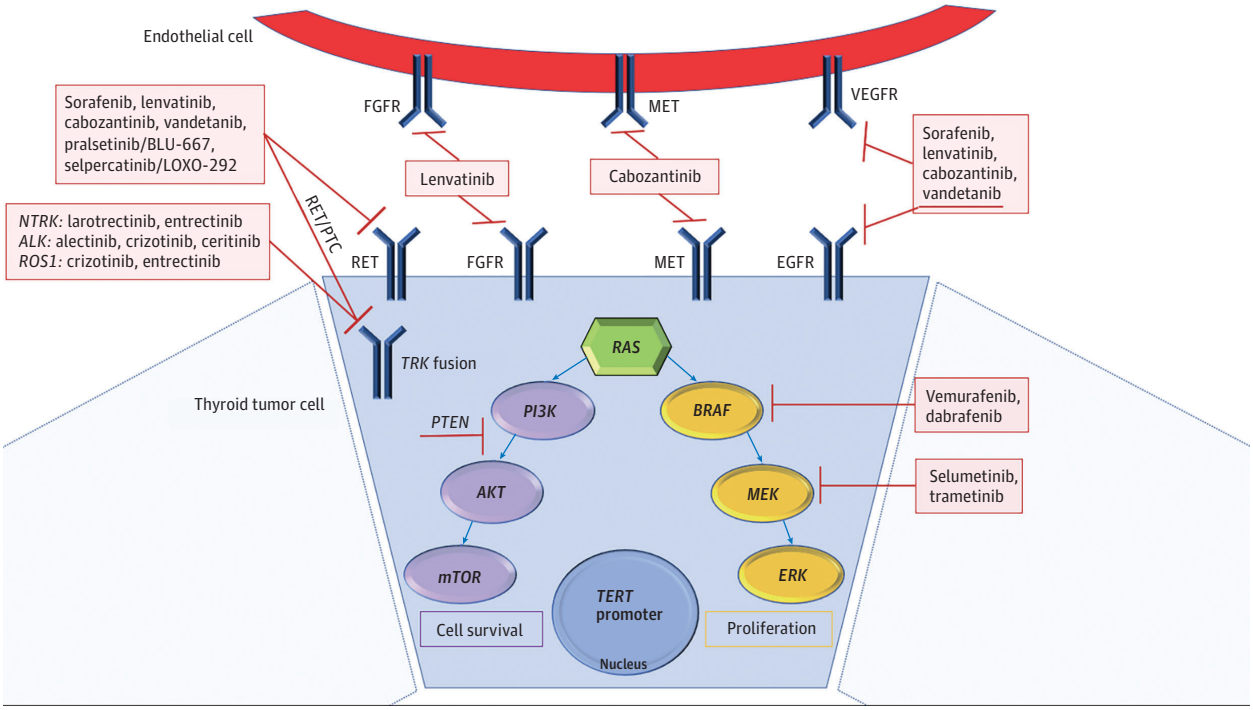
Oncogene-specific targeted therapy data indicate that treatment with this class of oral systemic medications can result in substantial reduction of tumor volume.[19] Those data suggest that early incorporation of these agents as neoadjuvant therapy in the treatment of patients with morbidly invasive disease may reduce the need

Table 1. Available Oncogene-Targeted Therapies

Oncogene target	Thyroid cancer type	Agent (clinical trial ID if open study)
NTRK fusion	Solid tumors, including PTC	Larotrectinib, all ages
		Entrectinib, 12 y and older
RET alterations and fusions	Solid tumors, including PTC or MTC	Pralsetinib/BLU-667 (NCT03037385)[9]
		Selpercatinib/LOXO-292 (NCT03157128,[11] NCT03899792[12])
ALK fusion	PTC	Crizotinib (NCT02034981)[13]
		Ceritinib (NCT02289144)[14]
		Alectinib (NCT03194893)[15]
		Ensartinib (NCT03155620)[16]
*BRAF*V600E	PTC	Vemurafenib (NCT03155620)[16]
		Dabrafenib-trametinib
Presumed *RET* alteration	MTC	Vandetanib
		Cabozantinib
Nonspecific multitargeted agents	DTC	Vandetanib (NCT01876784)[17]
		Cabozantinib (NCT03690388)[18]
		Sorafenib
		Lenvatinib

Abbreviations: DTC, differentiated thyroid cancer; MTC, medullary thyroid cancer; PTC, papillary thyroid cancer.

Figure 3. Commonly Activated Receptors and Signaling Pathways in Thyroid Cancer, With Molecular Targets of Systemic Therapy



The shaded areas at the bottom of the figure represent adjacent cells in a portion of a thyroid follicle. ALK indicates anaplastic lymphoma kinase; EGFR, epidermal growth factor receptor; FGFR, fibroblast growth factor receptor; MET, MET proto-oncogene receptor tyrosine kinase; PTC, papillary thyroid cancer; RET, rearranged during transfection; TRK, tropomyosin receptor kinase; and VEGFR, vascular endothelial growth factor receptor.

for surgery. In patients with DTC, once neoadjuvant tumor reduction is achieved, surgery and RAI therapy could then follow in an effort to achieve remission and avoid long-term use of systemic therapy. For patients with metastatic MTC or PDTC, the use of neoadjuvant oncogene-specific targeted therapies might allow for a reduction in tumor burden and permit a less morbid surgical resection of disease or even replace surgery because substantial surgical remission is rarely achievable in these patients. Those patients would be maintained on oral oncogene-specific targeted agents, with future studies needed to determine if this regimen would be lifelong or if the chemotherapy could induce senescence and ultimately be stopped.

The success of our proposed treatment paradigm shift is dependent on identifying patients with tumor-specific somatic oncogenic alteration. Both commercial and institute-specific somatic sequencing panels are available that can be used to screen for most gene alterations and fusions that are associated with thyroid cancer tumorigenesis. In the field of pediatrics, these targets include activating point alterations in *BRAF* (OMIM 164757) (30%) and fusions involving *RET* (30%), *NTRK3-ETV6* (OMIM 600618) (10%), *BRAF* (10%), and *ALK* (OMIM 105590) (5%) in PTC, as well as the germline activating *RET* alterations in almost 100% of pediatric MTC cases.[20] Testing for these somatic alterations can be performed on cytology specimens, fresh-frozen tissue obtained from small diagnostic biopsies in the setting of morbidly invasive disease, and formalin-fixed, paraffin-embedded samples. Testing on cell-free DNA, such as supernatant from fine-needle aspiration, ascites, effusions, or plasma, should be avoided because the sensitivity in patients with thyroid cancer appears to be low, and a negative result would not be conclusive. At a minimum, 0.1 to 0.2 mm^3 of tissue (approximately the size of a pencil tip) containing at least 20% tumor nuclei with proper preservation (ie, no decalcification) is required for most assays. The likelihood of pediatric patients with thyroid cancer (particularly PTC and MTC) having an identifiable, targetable gene fusion or alteration is high, although the limitations of each assay must be considered in test selection and interpretation.

The 2 cases reported herein provide examples of the potential surgical complications for a patient who presented with surgically morbid disease (case 1) as well as the potential benefit of incorporating neoadjuvant oncogene-specific targeted therapy into clinical practice (case 2). Although these cases are the exception and not the rule for most pediatric patients presenting with thyroid cancer, reducing or avoiding lifelong complications from therapy is a goal for all patients. In addition to these 2 cases, we have consulted on other patients and incorporated neoadjuvant therapy for 1 patient who presented with hypoxia secondary to extensive PTC-associated pulmonary metastasis, as well as another patient with MTC who had respiratory failure secondary to tumor-induced tracheal compression.[21] **Table 2** summarizes current clinical practice recommendations and the proposed therapeutic options for consideration of MKIs or oncogene-specific targeted neoadjuvant therapy, including (but not limited to) the following situations: (1) invasive DTC with recurrent laryngeal nerve paralysis, (2) invasive DTC or MTC with evidence of aerodigestive tract invasion, (3) PTC with high-burden

Table 2. Current Clinical Practice Recommendations, With Proposed Therapeutic Options

Clinical situation	Current clinical practice	Proposed therapeutic options
Differentiated thyroid cancer or MTC without extensive morbid regional invasion	Surgical resection (DTC and MTC), followed by selective use of radioactive iodine therapy	No recommended change to current guidelines
Differentiated thyroid cancer encasing neurovascular structures or the aerodigestive tract	Surgical resection, followed by radioactive iodine therapy	Neoadjuvant treatment with MKIs or oncogene-specific targeted therapy to induce medical regression of the tumor and/or resolution of hypoxia, followed by surgical resection and radioactive iodine therapy
Differentiated thyroid cancer presenting with hypoxia secondary to pulmonary burden	Surgical resection, followed by radioactive iodine therapy	
Medullary thyroid cancer encasing neurovascular structures or the aerodigestive tract	Surgical resection	Neoadjuvant treatment with MKIs or oncogene-specific targeted therapy. Surgery may be avoided based on the response to therapy and the likelihood of achieving surgical remission

Abbreviations: DTC, differentiated thyroid cancer; MKI, multitargeted kinase inhibitor; MTC, medullary thyroid cancer.

pulmonary metastasis presenting with hypoxia, and (4) widely metastatic DTC, MTC, or PDTC with encasement of the great vessels.

Recently, the Children's Oncology Group opened a phase 2 study[22] of larotrectinib for children with previously untreated *TRK* fusion solid tumors, including pediatric thyroid cancer. That prospective study will define the benefits and risks of medical therapy for children and adolescents with thyroid cancer for whom surgery carries a high risk of morbidity. In addition, the National Cancer Institute and Children's Oncology Group Pediatric MATCH is a phase 2 study[16] that offers access to several agents based on the presence of predetermined molecular lesions, including *BRAF* alterations (vemurafenib) and *ALK* fusions (ensartinib), and soon to include *RET* alterations or fusions (LOXO-292). A limitation of the Pediatric MATCH trial is the exclusion of patients with previously untreated tumors. The success of these trials in studying pediatric thyroid cancer will depend on referral of patients to pediatric oncology centers for screening, enrollment, and management. Additional clinical trials of MKIs and oncogene-specific targeted therapies are needed in an effort to define which pediatric patients would benefit from systemic therapy, as well as how to incorporate these powerful new drugs into clinical practice (Table 2).

Conclusions

Standard therapy for thyroid cancer in children involves surgical resection of gross disease (for patients with DTC and MTC), followed by RAI therapy in patients with invasive DTC. With the emergence of MKIs, as well as oncogene-specific targeted therapy, there is an opportunity to incorporate these systemic therapies into clinical practice for patients with refractory anatomically progressive disease after standard therapy has failed. In addition, it may be time for a paradigm shift (Table 2) in which medical therapy with MKIs or oncogene-specific targeted agents before surgery and RAI therapy may maintain low disease-specific mortality and optimize outcomes by reducing treatment-associated complications for patients who initially present with morbidly invasive thyroid cancer at diagnosis.

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