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(REVIEW ARTICLE)

NTRK-fusion detection in thyroid and salivary gland cancer offers a targeted therapy with NTRK-inhibitor

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Abstract

NTRK-fusion in cancer is rare but it offers targeted therapy with NTRK-inhibitor. NTRK fusion is not a point mutation. NTRK fusion is an oncogenic driver, NTRK mutation is not an oncogenic driver. Patients with NTRK point mutation do not respond to NTRK-targeted therapy. NTRK fusion was detected in secretory carcinoma. Secretory carcinoma was a new entity, first described in 2010, classified by NTRK-fusion. It is often misdiagnosed, and standard pathology often fails to distinguish it from another histology subtype of salivary gland carcinoma, so its frequency can be higher than has been reported. Therefore, different examinations are needed in order to obtain a correct diagnosis. In thyroid gland carcinoma, NTRK fusion-positive carcinomas are associated with clinically aggressive disease with a high metastatic rate. Therefore NTRK-fusion test should be performed in thyroid cancer patients with recurrence and unresectable disease, metastatic thyroid cancer, Radioactive Iodine (RAI)-refractory disease, and invasive disease. Immunohistochemistry with antibody against TRKA, TRKB, and TRKC can be used to identify TRK protein expression in salivary gland cancer so this test can be used for screening in all salivary gland cancers. NGS or FISH are tools that can be used to confirm NTRK fusion. Detection of NTRK fusion allows new hope for cancer patients with refractory therapy.

Keywords: Cancer; Head and neck cancer; Secretory carcinoma; NTRK fusion

1. Introduction

NTRK fusion in cancer refers to a specific genetic alteration where a portion of the NTRK (Neurotrophic Tyrosine Receptor Kinase) gene becomes fused with another gene, often as a result of chromosomal rearrangements. NTRK genes, including NTRK1, NTRK2, and NTRK3, encode proteins (TRKA, TRKB, and TKRC) that are involved in cell signaling pathways related to nerve growth and development [1]. NTRK fusions are typically somatic gene arrangement, meaning they arise specifically in the cancer cells themselves rather than being inherited from the germline (i.e., the DNA passed down from parents to offspring) [2]. Somatic gene arrangement occur during a person's lifetime and are not present in every cell of the body [3]. In the context of cancer, somatic gene arrangement in NTRK genes can lead to the fusion of NTRK with other genes. This fusion results in the production of abnormal NTRK fusion proteins, which can have a role in promoting the growth and progression of certain types of cancer [4]. While NTRK fusions themselves are considered rare events across all cancer types, they have been identified in a variety of malignancies, including certain types of pediatric cancers, sarcomas, and some solid tumors in adults, like non-small cell lung cancer, colorectal cancer, and thyroid cancer [5]. The prevalence of NTRK fusions varies among different cancer types. These fusions have some characteristics in distribution, that are high frequency in some very rare neoplasms, and extremely lower frequencies in more common tumors. Some rare cancers that frequently have NTRK fusion are infantile fibrosarcoma, congenital mesonephroma, secretory mammary carcinoma, and the analogous neoplasm in salivary glands. Based on research conducted by Marchetti et al. [6], the highest prevalence of NTRK fusion in adults (over 18 years) was in salivary gland

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cancers (2.43%), soft tissue sarcomas (1.27%), and thyroid tumors (1.25%). Whereas, according to a systematic review conducted by O'Haire et al. [2], the highest prevalence of NTRK fusion is found in rare cancers such as infantile fibrosarcoma (70.37%), secretory carcinoma of the breast (90.91%) and secretory carcinoma of the salivary gland (range 83.33–89.66%).

The discovery of NTRK fusions has led to the development of targeted therapies known as NTRK inhibitors [7]. NTRK inhibitors are drugs designed to specifically block the abnormal activity of the NTRK fusion proteins [8]. One such example is larotrectinib (Vitrakvi), which was one of the first FDA-approved NTRK inhibitors [9]. Another example is entrectinib (Rozlytrek). These drugs specifically target and block the activity of the abnormal NTRK fusion protein, inhibiting the downstream signaling pathways and halting cancer cell growth. Targeted therapies for NTRK fusion-positive cancers have shown remarkable efficacy and have led to significant clinical responses in some patients [10, 11]. Based on the study conducted by Drilon [10], the response rate of Larotrectinib was 75%, and 55% of patients proven to remain free from cancer progression. They have shown promise as highly effective treatments for patients with NTRK fusion-positive cancers, leading to significant tumor shrinkage and improved clinical outcomes [12]. Clinical trials and real-world evidence have shown promising results regarding response rates and prolonged disease control in patients with NTRK fusion-positive cancers. However, NTRK fusion-positive cancer is rare and has different prevalence in each different type of cancer, so molecular testing is essential to accurately identify patients who may benefit from these targeted treatments.

2. Review Content

2.1. The difference between NTRK fusion and point mutation

NTRK fusion is distinct from a point mutation and plays a crucial role in developing certain cancers. The term "NTRK fusion" refers to a genetic alteration where segments of the NTRK gene become connected to another gene due to chromosomal rearrangements, where a portion of an NTRK gene becomes fused with another gene [13]. This fusion event can lead to the formation of a chimeric gene, which encodes a hybrid protein characterized by ligand-independent constitutive activation of the TRK kinase [4]. TRK fusion protein has the potential to drive the growth and progression of cancer [14]. These fusion proteins continuously activate signaling pathways that promote cell proliferation, survival, and tumor development [15]. This makes NTRK fusion an oncogenic driver, meaning it contributes significantly to the initiation and maintenance of cancer [1]. As a result, cancer cells with NTRK fusions become highly dependent on these abnormal signaling pathways [16].

In contrast, an NTRK mutation refers to changes in the DNA sequence of the NTRK gene that involve single nucleotide substitutions, deletions, or insertions [17]. While NTRK mutations may alter the function of the TRK receptors, they are not always associated with oncogenic activity. In many cases, NTRK mutations are not potent enough to drive cancer development on their own, and they may not be the primary cause of the disease [18]. However, patients with NTRK point mutations, which are not as strongly associated with oncogenic activity, typically do not respond well to NTRK-targeted therapy [19]. In addition, the effectiveness of TKI inhibitors at the mutation point is still unclear [20]. Even some point mutations are resistant to NTRK inhibitor treatment [21]. On the contrary, NTRK fusion-positive cancers tend to be more responsive to NTRK inhibitors due to the direct involvement of the fusion protein in driving the malignancy [22, 23].

In summary, NTRK fusion involves the fusion of the NTRK gene with another gene, leading to the creation of oncogenic TRK fusion proteins that drive cancer growth. While NTRK mutations are changes in the NTRK gene's DNA sequence that may not always be oncogenic drivers. Patients with NTRK fusions can benefit from targeted therapy with NTRK inhibitors, while those with NTRK point mutations are less likely to respond to such treatment. So, not all NTRK genetic change can end up becoming cancer and responds to specific targeted therapy such as NTRK inhibitor. This highlights the importance of accurately identifying the specific genetic alteration in a patient's cancer because the differences in gene arrangement can end up in different suitable treatments for patients.

2.2. NTRK fusion in secretory carcinoma

NTRK fusion has been identified as a defining characteristic in a distinct type of cancer known as secretory carcinoma (SC) [24]. Secretory carcinoma is a relatively newly recognized entity within the spectrum of cancers. Secretory carcinoma was first described in 2010, marking it as a recent addition to the list of known cancer types [25]. It is a rare malignancy that has unique features and characteristics that distinguish it from other types of cancer. One of the key defining features of secretory carcinoma is the presence of NTRK fusions [26]. In secretory carcinoma, NTRK fusions

play a pivotal role in the development of the cancer. The presence of these fusions appears to be a key genetic event that contributes to the unique characteristics of secretory carcinoma [27].

Secretory carcinoma is a distinct type of cancer that poses diagnostic challenges due to its resemblance to other histological subtypes of salivary gland carcinoma [28]. Histological examination, which involves the microscopic analysis of tissue samples, is a fundamental tool in diagnosing various cancers. Histologically, secretory carcinoma consists of vesicular nuclei and abundant eosinophilic vacuolated cytoplasm arranged in microcystic, papillary, cystic, solid, macrocystic, and tubular patterns. These histological-specific characteristics can overlap with those of other salivary gland carcinomas, making it difficult to distinguish using traditional pathology methods alone. The distinct features of secretory carcinoma can be subtle and standard pathological examinations may not always accurately differentiate it from other types of salivary gland cancers [29]. According to the histological picture, SC is often difficult to distinguish from acinic cell carcinoma (AciCC), polymorphous adenocarcinoma (PAC), and intercalated duct-type intraductal carcinoma (IDC) [26]. As a result, secretory carcinoma is often misdiagnosed and it can lead to underreporting of secretory carcinoma cases and hinder our understanding of its true prevalence [30]. The true prevalence of secretory carcinoma could potentially be higher than what has been reported [31]. The misdiagnosis of secretory carcinoma is not uncommon and it underscores the need for advanced diagnostic techniques and molecular analyses to accurately identify this cancer subtype. Molecular testing methods, such as genetic profiling and immunohistochemistry, can provide additional information about the genetic alterations and protein expression patterns associated with secretory carcinoma. These techniques can aid in distinguishing secretory carcinoma from other salivary gland carcinomas and help improve diagnostic accuracy [32]. The discovery of secretory carcinoma as a distinct cancer type based on NTRK fusions highlights the rapid advances in molecular diagnostics and our understanding of the genetic drivers of cancer. It also underscores the importance of precision medicine, where treatments are tailored to the specific genetic alterations present in a patient's tumor.

2.3. NTRK fusion in thyroid carcinoma

NTRK fusion in thyroid carcinoma (TC) turns out to have a high incidence rate in certain conditions. Therefore, NTRK fusion test should be performed in several tumor conditions, such as:

2.3.1. Thyroid cancer patients with recurrence and unresectable disease

A case presentation showed the success of NTRK inhibitor treatment in recurred TCs. Several patients underwent thyroidectomy and central neck dissection and some of them had metastasectomy and radiotherapy procedures. However, after several years, they developed recurrence and metastases, especially in the lungs. They were positive for NTRK fusion and then treated with NTRK inhibitor drug. This treatment was more effective than previous standard treatments because the drugs inhibit the exact oncogenic driver [33]. NTRK fusion-positive TC is associated with high recurrence (82%) although the patient has received total thyroidectomy and radioactive iodine (RAI) treatment [34].

2.3.2. Metastatic thyroid cancer

Thyroid cancer harboring NTRK fusion is associated with a high metastatic rate. All NTRK fusion-positive thyroid cancers can invade the cervical lymph node and lymphovascular systems extensively [34]. Another study stated that 95% of patients with NTRK fusion-positive experienced lymphovascular invasion and as many as 79% experienced lymph node metastases [35]. In pediatric PTC, NTRK fusion-positive has correlated with a high association with distant metastasis and lung metastases [36]. Thus, it can be concluded that the characteristic of NTRK fusion-positive cancer is that it easily metastasizes.

2.4. Radioactive Iodine (RAI)-refractory disease and papillary thyroid carcinoma

RAI is an ideal choice to treat distant metastases. However, there is adaptation in some patients so that tumors no longer trap iodine and this results in (RAI)-refractory disease. In RAI-R disease, tumors become resistant and can no longer receive this treatment. Even some differentiated thyroid carcinomas (DTC) that become RAI-R are mainly due to the upregulation of TRK that can support cancer growth [37]. Fazeli et al. [39] identify NTRK fusion in advanced and RAI-refractory disease. A total of 36 people with RAI-R were identified as NTRK fusion-positive thyroid cancer (TC). Out of 36 patients, 28 (78%) were papillary thyroid carcinoma (PTC). PTC is the one of DTCs. Besides that, 77% of PTC had distant metastases. This is in line with research conducted by Eszlinger et al. [38], which mention that NTRK fusions are more commonly found in patients with RAI-R DTC, metastatic TC, or advanced TC. However, the presence of NTRK fusions in TC is rare and the frequency ranges from 2.3 to 3.4% in adults. While in pediatrics, NTRK fusions-positive TC are more or less eight times more common than in adults (18.3% and 25.9% of all TC) [39]. Therefore, pediatric patients, patients with RAI-R disease, or DTC should be undergoing NTRK testing [40].

2.5. Invasive thyroid carcinoma

In pediatric PTCs, the presence of NTRK fusion makes cancer more invasive. In addition, compared to other mutations, pediatric tumors harboring NTRK fusion are the most invasive tumors [41]. Cytologically, thyroid carcinoma with NTRK fusion-positive indicates the presence of a multifocal tumor with extensive lymphovascular and extrathyroidal invasion [42].

From the explanation above, it can be concluded that NTRK fusion is often found in recurrence and unresectable, metastasis, RAI-R disease, and invasive TC. This is because NTRK fusion-positive carcinomas are associated with clinically aggressive diseases with a high metastatic rate and most of them are not responsive to several standard treatments [34]. For this reason, it is important to perform an NTRK fusion examination on these conditions to determine the proper treatment for the patient.

2.6. Detection of NTRK fusion

Conventional cancer therapies, such as chemotherapy, radiation, and surgery, are the standard treatments used to combat cancer [43]. However, not all patients respond favorably to these treatments, and some cancers can become resistant over time, leading to disease progression and limited treatment options [44, 45]. In such cases, patients may face challenges in finding effective treatments that can control their disease.

The detection of NTRK fusions in cancer patients offers a renewed sense of hope, particularly for those who have not responded to or have become resistant to conventional therapies. For patients with NTRK fusion-positive cancers who may have previously felt discouraged due to limited treatment options, the availability of targeted therapy can be transformative. NTRK fusions represent a unique genetic alteration that results in the production of abnormal fusion proteins, often referred to as TRK fusion proteins [46]. These fusion proteins are constitutively active, leading to continuous signaling that promotes cancer growth [23]. Assessing TRK protein expression through immunohistochemistry is an essential initial step to identifying potential candidates for NTRK-targeted therapies, as their expression can be an indicator of potential NTRK fusions [47]. If TRK proteins are overexpressed, it suggests the possibility of an NTRK fusion-positive cancer, which might respond well to targeted treatment with NTRK inhibitors [48]. NTRK inhibitors are designed to specifically block the abnormal activity of the fusion proteins that result from NTRK gene fusions. By doing so, they interrupt the signaling pathways that promote cancer cell growth and survival, ultimately inhibiting tumor progression. Clinical trials and real-world evidence have shown that NTRK inhibitors can lead to significant and lasting responses in patients who were previously unresponsive to conventional therapies [4]. This means that even in cases where other treatments have failed, patients now have a chance at disease control and improved quality of life. Furthermore, the development of targeted therapies like NTRK inhibitors exemplifies the potential of personalized medicine. By tailoring treatments to the specific genetic alterations driving a patient's cancer, these therapies can offer more effective and less toxic options compared to broad-spectrum treatments like chemotherapy [49]. This discovery has opened up new avenues for targeted treatment approaches, providing an alternative strategy for patients who have exhausted traditional therapeutic options. However, to start NTRK inhibitor therapy, an NTRK fusion examination must be done.

Immunohistochemistry (IHC) can be employed to identify the expression of TRK proteins, which are the products of the NTRK genes. This information can indirectly suggest the presence of NTRK fusions. Immunohistochemistry involves the use of antibodies that bind specifically to target proteins [50]. In the case of TRK proteins, specific antibodies can be applied to tissue sections obtained from biopsy or surgical specimens. If TRK proteins are expressed in the tissue, the antibodies will bind to these proteins, leading to a visible color reaction that can be observed under a microscope [51]. It was reported that the immunostaining pattern of a chimeric protein is influenced by the ordinary localization of the protein of the fusion partner gene [52]. The NTRK fusion gene not only consists of one gene, but there are 3 different genes as well, that are NTRK1, NTRK2, and NTRK3. This gene difference allows many possible fusion pairs to occur, causing the detection of gene fusion to be complex. Therefore, IHC detection brings several advantages like faster results, lower cost, wide availability, and requires a smaller amount of tissue for examination [53]. However, it's important to note that immunohistochemistry for TRK protein expression is an indirect method and does not directly detect the presence of NTRK fusions. Instead, it identifies the presence of TRK proteins, which can be indicative of NTRK fusion events. The limitation of IHC is that TRK protein is physiologically expressed in nerve tissue and smooth muscle, so it can cause false positives [54]. IHC testing uses antibodies to bind to proteins, so the reliability of IHC depends on how specific antibodies are used. Some studies still mention that IHC examination does have high sensitivity, but has different specificity. In addition, studies prove that there is still a possibility that IHC-positive TRK is not only caused by NTRK fusion [52]. IHC also showed a high false-positive rate for the NTRK fusion [55]. Therefore, if TRK protein expression is detected, further molecular testing may be performed to confirm the presence of NTRK fusions [54]. Two

common methods used to identify NTRK fusions are next-generation sequencing (NGS) and fluorescence in situ hybridization (FISH), with FISH being an alternative when NGS is unavailable.

3. Conclusion

The detection of NTRK fusions in cancer patients who are refractory to conventional therapies brings a renewed sense of hope and possibility. Targeted therapies like NTRK inhibitors provide an innovative approach to treatment, offering the potential for meaningful responses and improved outcomes for individuals who have faced limited options in the past. Given that the incidence of NTRK fusion is quite rare, to start NTRK inhibitor therapy, an IHC examination is needed which is then confirmed with NGS or FISH. This breakthrough underscores the ongoing advancement in cancer research and the promise of precision medicine in transforming cancer care.

Compliance with ethical standards

Disclosure of conflict of interest

There is no conflict of interest to be disclosed.

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