JOURNAL OF ADOLESCENT AND YOUNG ADULT ONCOLOGY
Volume 9, Number 2, 2020
Mary Ann Liebert, Inc.
DOI: 10.1089/jayao.2019.0098

Perspective

Overdiagnosis of Juvenile Thyroid Cancer: Time to Consider Self-Limiting Cancer

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Overdiagnosis of thyroid cancer is now recognized as a worldwide problem. Recent data revealed that juvenile thyroid cancers grow rapidly and initially show the aggressive features; however, most of them gradually stop proliferating due to their self-limiting growth. When this self-limiting characteristic of juvenile thyroid cancer is taken into account, ultrasonography (US) screening of young generations should be avoided since early detection of thyroid cancer in the young is harmful. Furthermore, we should reconsider the desirable timing of surgery for juvenile thyroid cancer and should search for the true origin of lethal thyroid cancer.

In many countries, overdiagnosis of thyroid cancer is now a serious problem, and overuse of US is recognized as one of its causes.[1,2] The number of patients who might be affected by overdiagnosis depends on physicians' attitude toward papillary thyroid microcarcinoma (PTM). For many years since the multistep carcinogenesis theory was established as the main theory on thyroid carcinogenesis, early detection and treatment have been regarded as golden rules.[3] Thus, until recently, almost all patients with PTM detected by US were encouraged to undergo surgery.

Recent studies on thyroid cancer from developed countries showed a discrepancy between an increasing incidence and stable mortality.[4] They proved that early treatment of small thyroid cancer does not lead to decreased mortality. The concept that small and indolent thyroid tumors turn into more aggressive and lethal ones, as hypothesized in the classical concept of multistep carcinogenesis, is no longer considered true. To understand this phenomenon correctly, we should take a careful look at the natural history of thyroid cancer (Fig. 1).[5]

Thyroid cancers in children show paradoxical clinical features. They are usually recognized as large tumors with rapid growth and are often accompanied by local and distance metastases. Furthermore, their recurrence rate after surgery is much higher than in adults. However, the associated prognosis is excellent, with a life span survival rate of >95%.[6] These features of thyroid cancers in children, which show a marked contrast to those in adults, have been puzzling clinicians for many years.

Since the accident at the Fukushima Daiichi Nuclear Plant in 2011, the Fukushima Health Management Survey (FHMS), which targeted ~380,000 children, has been ongoing and it has generated some surprising results that might help answer the aforementioned question.[7,8] In the FHMS, >200 children have been diagnosed with thyroid cancer by US and fine needle aspiration cytology so far, confirming that papillary carcinoma is a common childhood phenomenon. The distribution of the patients' age suggested that these cancers start growing before adolescence and grow rapidly when children are in their teens. In contrast, the tumors' growth rate is negatively correlated with their size; thus, it is likely that they show self-limiting growth.[9]

Data from an observation study indicated that PTMs in the patients >40 years old showed limited growth and a part of them even shrank during the observation.[10] These data suggest that thyroid cancers detected by US in children are self-limiting. Although they show rapid growth in patients in their teens or 20s, the majority of them stop proliferation after a few decades and appear as PTMs. Despite these characteristics, they are truly cancer from pathologists' point of view, since >80% of thyroid cancers found in the FHMS showed invasion to the surrounding tissues or were accompanied by local or distant metastasis; however, they are not lethal malignancies but indolent tumors from a prognostic point of view.[11]

In summary, juvenile thyroid cancers grow rapidly and initially show the aggressive feature of invasion or metastasis; however, they are associated with an excellent prognosis because they gradually stop proliferating due to their self-limiting growth. Therefore, they can be regarded as self-limiting cancers, which are difficult to explain with the classical concept of multistep carcinogenesis whereby every indolent tumor has a risk of evolving into an aggressive one.

Some researchers describe PTM as an indolent lesion of epithelial origin or innocent cancer.[12] However, it is not appropriate to describe all juvenile PTMs using these terms. Although presented as very rare cases, some juvenile thyroid cancers cause cancer death when patients do not receive appropriate therapy. Self-limiting cancer can kill patients when showing rapid growth before growth arrest. Cases with rapid growth in childhood, or those showing a poor response to radioactive iodine therapy, may progress to cancer death regardless of the cancer's self-limiting property. Thus, we

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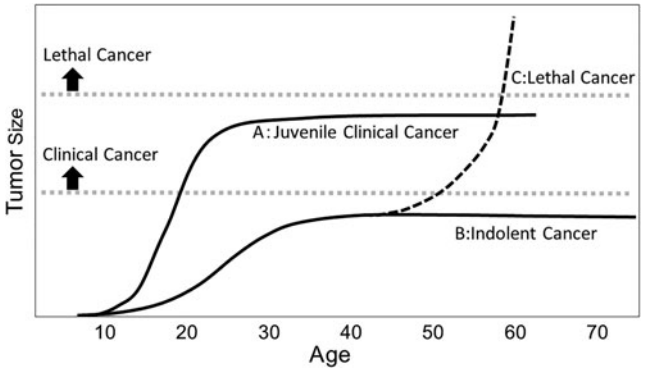

FIG. 1. Fate of juvenile thyroid cancers. Juvenile thyroid cancers start proliferating before adolescence and show rapid growth in patients in their teens and 20s. A limited number of them appear as clinical cancers in the young **(A)**. The rest become indolent small cancers **(B)**. It is rare, if occurring at all, for such an indolent cancer to become lethal **(C)**.

might not be able to describe proliferating juvenile PTMs as innocent or indolent until they stop growing.

The main discussion point regarding the existence of self-limiting thyroid cancer is whether PTMs that initially stop growing actually start proliferating again to become lethal cancer after several decades. From a molecular point of view, it is very unlikely that indolent thyroid cancer cells turn into poorly differentiated or anaplastic cancer cells. First, genetic alternations, observed at a high prevalence in differentiated thyroid carcinomas, such as *RET/PTC*, P*AX8-PPARγ1*, and *BRAF* point mutation, have never been detected or are detected at a much lower prevalence in anaplastic carcinomas.[13–15] Second, some recent studies using whole-exome sequencing proved that coexisting differentiated and anaplastic carcinomas share only a limited number of common genetic alternations while each carcinoma possesses many independent ones.[16,17] These data suggest that although these two coexist and might share a common origin, they evolved independently.

Conclusive data have not been presented; however, we should remember that at least at present, even though a vast amount of data from observation trials of PTMs has already been accumulated, not a single case that became lethal or was accompanied by anaplastic transformation has been reported.[18,19] Thus, it is very exceptional, if occurring at all, for a patient to die from PTMs. Considering these data, significant modifications were made to the American Thyroid Association (ATA) guidelines, American Joint Committee on Cancer (AJCC) staging system, and WHO classification, to reduce overdiagnosis and overtreatment of thyroid cancers.[20–22]

When the existence of self-limiting thyroid cancer is taken into account, the following three issues need to be considered. First, we should remember that early detection of thyroid cancer in the young is harmful and US screening of young generations should be avoided. In fact, there are no definite data showing that early detection of thyroid cancer, for example, by US, reduces mortality or improves the quality of life. Early detection of self-limiting thyroid cancer directly leads to the harm of overdiagnosis.[23] It can be harmful for patients not only in physiological ways such as surgical complications, but also in psychological and social ways to be regarded as patients with juvenile cancer, which is recognized as lethal disease in general.[24] There is a prevailing opinion that thyroid US screening is necessary after a nuclear plant accident to reduce residents' anxiety. However, we should remember that it is a matter of medical ethics, since such a relief is provided at the sacrifice of children's health.

Second, in further investigations, we should reconsider the desirable timing of surgery for juvenile thyroid cancer. Self-limiting cancers grow rapidly and often spread outside the thyroid in the young but are likely to stop growing. Thus, surgery too early not only results in unnecessary treatment but also leads to an increasing recurrence rate when small surgery is performed in the tumor's rapidly growing phase. In the future, accumulating data from observation trials targeting young patients might help to draw a conclusion.

Third, PTMs are not likely to be a major source of lethal thyroid cancers. Furthermore, normal thyrocytes are not likely either, because radioactive iodine cannot induce thyroid cancer in adults.[25] The true origin of lethal cancers should be searched for intensively in further investigations.

Author Disclosure Statement

No competing financial interests exist.

Funding Information

No funding was received for this article.

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