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. 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. 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. 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 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. 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...
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, PAX8-PPARγ1, and \( BRAF \) point mutation, have never been detected or are detected at a much lower prevalence in anaplastic carcinomas. Second, some recent studies using whole-exome sequencing proved that coexisting differentiated and anaplastic carcinomas share only a limited number of common genetic alterations while each carcinoma possesses many independent ones. 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. 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.

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. 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. 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. The true origin of lethal cancers should be searched for intensively in further investigations.

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