DOI: 10.1111/cen.14746

LETTER TO THE EDITOR

WILEY

# Secondary thyroid carcinoma in survivors of childhood cancer: A need to revise current screening recommendations

Thyroid cancer is the most common secondary malignancy for survivors of childhood cancer, with radiation exposure before age 18 being the most significant risk factor. Current guidelines from the Children's Oncology Group recommend yearly physical examination to palpate for thyroid nodules.[1] Whilst other societies recommend periodic thyroid ultrasound,[2–5] further evaluation with fine-needle aspirate (FNA) is typically not considered for nodules less than 10 mm in diameter. We describe a case series of five patients (Table 1) with papillary thyroid carcinoma (PTC) following radiation exposure, all with nodules <10 mm (and some <5 mm) and three with metastatic disease. These nodules were all impalpable and only detected by surveillance ultrasound. If current guidelines were followed, these cases would have remained undetected until a more advanced stage, highlighting the inadequacy of current recommendations regarding monitoring of this high-risk patient group. It is our practice to perform surveillance thyroid ultrasonography every 2 years, commencing 2 years after radiation exposure,[6] with FNA of suspicious lesions regardless of size. We have a low threshold to offer total thyroidectomy (TTx) and bilateral central lymph node dissection (CLND).

Case 1 received 12 Gy total body irradiation (TBI) at age 10 for relapsed acute lymphocytic leukaemia (ALL) with an initial diagnosis 5 years earlier. On surveillance with thyroid ultrasound, she had a 5.8 mm nodule 12 years after her initial radiotherapy. FNA confirmed PTC. TTx with CLND was performed, demonstrating multifocal bilateral PTC (largest 7 mm) and no lymphovascular invasion.

Case 2 received 50 Gy right parameningeal targeted radiotherapy for nasopharyngeal rhabdomyosarcoma at age 4. At age 11, recurrence involving the right internal jugular vein with atrial propagation was resected, with the delivery of 41 G right supraclavicular fossa radiotherapy. An ultrasound 7 years later identified a left 3 mm thyroid lesion with suspicious cervical lymphadenopathy confirmed as metastatic PTC on FNA. She underwent TTx with bilateral CLND and left lateral neck dissection confirming bilateral PTC (3 mm on left and 2 mm on right) and both lateral and central lymph node involvement.

Case 3 received 23 Gy craniospinal radiation plus an additional 32 Gy targeted posterior fossa radiation for medulloblastoma at age 5. Nine years later, a 7 mm nodule was found on thyroid ultrasound. FNA showed atypical follicular pattern (Bethesda-B4). TTx and CLND were performed, with histologic evidence of multifocal PTC, lymph node involvement, and extrathyroidal invasion to adjacent skeletal muscle and one small vessel.

Case 4 underwent an allogeneic haemopoietic stem cell transplant (HSCT) for relapsed ALL at age 11 (initially diagnosed at age 6) and received 12 Gy TBI. A 3-mm nodule was detected on ultrasound 11 years later. FNA was suspicious for PTC (B5) and he underwent TTx and CLND. Pathology confirmed PTC with no lymph node involvement. Temporary left recurrent nerve palsy and hypoparathyroidism both resolved in under 3 months.

Case 5 was diagnosed with high-risk ALL at age 4 and had HSCT with 12 Gy TBI conditioning. Six years later, a 9-mm nodule on ultrasound was confirmed as PTC. Initial left hemithyroidectomy elsewhere demonstrated multifocal PTC. Subsequent completion of right hemithyroidectomy and right CLND yielded two microscopic foci of PTC and negative nodes. Four years later, he required left CLND for multiple lymph node recurrences up to 7 mm, detected by rising thyroglobulin and ultrasound.

All cases had postthyroidectomy surveillance with diagnostic whole-body I124 scans. Case 5 required initial ablative I131 (1600 MBq/43 mCi) for positive uptake in the neck (~2%). Subsequent imaging has shown no uptake. As per our standard surveillance (and international guidelines),[3,6–9] all cases have annual monitoring with recombinant thyroid-stimulating hormone-stimulated thyroglobulin levels and neck ultrasound. No late recurrences have been detected.

There is debate in the literature regarding both necessity of routine surveillance and the optimal modality for screening, citing surveillance as potentially exposing patients to unnecessary harms and avoidable distress.[3,4,10] Over the past 20 years, we have undertaken surveillance of 339 patients postradiation exposure, utilizing 2-yearly ultrasound, with an abnormality detected in 129 (38%). Of those 129, early ultrasound both identified a need for FNA in solid nodules >4 mm and defined the requirement for surgery in 61/129 (47%). Forty-five out of the 61 were found to have thyroid cancer (74% of total thyroidectomies and 35% of all those with abnormal thyroid ultrasound). The remainder were flagged for ongoing surveillance. Our cases address the rationale for a more sensitive screening tool than palpation and reasons for being more aggressive with surveillance and surgical strategy even when cytology is equivocal. We believe our data support that the benefit of ultrasound screening in a high-volume centre outweighs the risk, as we

**TABLE 1** Summary of case details

| Case # | Primary malignancy | Sex | Age of primary malignancy (years) | Radiation received (dose in Gy) | Ultrasound findings | Histology of thyroid malignancy | TNM staging | Time from first radiation to the onset of thyroid malignancy (years) |
|---|---|---|---|---|---|---|---|---|
| 1 | ALL (relapse) | Female | 10 | TBI (12 Gy) | 5.8 mm single nodule | Papillary thyroid carcinoma | $T_1N_0M_0$ | 12 |
| 2 | Nasopharyngeal rhabdomyosarcoma<br>Cardiac rhabdomyosarcoma | Female | 411 | Parameningeal (50 Gy)<br>Supraclavicular fossa (41 Gy) | 3 mm single nodule and lateral neck nodes | Metastatic papillary thyroid carcinoma | $T_1N_{1b}M_0$ | 14 |
| 3 | Posterior fossa medulloblastoma | Female | 5 | Craniospinal (23 Gy)<br>Posterior fossa (32 Gy) | 7 mm single nodule | Metastatic papillary thyroid carcinoma | $T_1N_{1a}M_0$ | 9 |
| 4 | ALL (relapse) | Male | 11 | TBI (12 Gy) | 3 mm single nodule | Papillary thyroid carcinoma | $T_1N_0M_0$ | 11 |
| 5 | ALL | Male | 4 | TBI (12 Gy) | 9 mm single nodule | Metastatic papillary thyroid carcinoma | $T_1N_{1a}M_0$ | 6 |

Abbreviations: ALL, acute lymphocytic leukaemia; Gy, Gray (unit of ionizing radiation); TBI, total body irradiation; TNM staging: T, tumour size, N, lymph nodes, M, distant metastasis.

have demonstrated a high level of clinically significant malignancy (74%) in those selected for thyroidectomy and a low rate of complications. The benefit of early diagnosis and cure of a potentially life-threatening disease is likely to outweigh potential psychological distress from screening. Using the same high-volume surgeon and liberal transplantation of parathyroid glands, complications of treatment in our cohort have remained low, with no cases of permanent laryngeal nerve palsy and no permanent hypoparathyroidism (approximately 25% with temporary hypoparathyroidism resolving over 1–6 months).

Radiation-induced thyroid cancer is suspected to be more aggressive than spontaneous thyroid cancer and screening guidelines should reflect this.[11,12] Our data for a high-risk group challenge current assumptions in the literature that small nodules have a lower risk of malignancy and that very small lesions <5 mm may remain quiescent and are of negligible metastatic potential. These cases highlight the impalpable nature of smaller thyroid nodules and cervical lymphadenopathy, recommend utilization of screening ultrasound and indicate a need to revise clinical guidelines for surveillance of paediatric and adolescent thyroid cancer post-radiation exposure.

## ACKNOWLEDGEMENT

Open access publishing facilitated by The University of Melbourne, as part of the Wiley - The University of Melbourne agreement via the Council of Australian University Librarians.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

## DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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