

Secondary thyroid cancer among childhood cancer survivors. A single institute experience.

Muraca M., Bagnasco F., Caruso S., Morsellino V., Cabria M.*, Maghnie M[^], Haupt R.

Epidemiology and Biostatistics Unit, Giannina Gaslini Institute, Genoa, Italy

*Nuclear Medicine Unit, Galliera Hospital, Genoa, Italy

[^]Endocrine Unit, Giannina Gaslini Institute, University of Genoa, Italy



BACKGROUND:

Childhood cancer survivors (CCS) are at increased risk of developing secondary malignant neoplasms (SMN) including secondary thyroid cancers (STC). Radiotherapy is one of the main risk factors for the development of SMN. Also alkylating agents are used for the treatment of childhood cancers and are associated with the risk of several late adverse effects including SMN.

OBJECTIVES:

To evaluate the frequency and cumulative risk of STC among CCS in follow-up at the Istituto Giannina Gaslini (IGG), and identify treatment related risk factors.

METHODS:

Cancer patients treated at IGG between 1975 and 2013, who had reached the elective end of therapy at least 2 years before were eligible for this study.

For each survivor the treatment history was collected including fields and doses of radiotherapy, as well the cumulative alkylating agent exposure calculated as cyclophosphamide equivalent dose (CED)¹.

At follow-up the physical exam of thyroid gland was scheduled for all subjects, and the ultrasound evaluation was performed to all CCS previously irradiated to fields potentially involving the thyroid as well to survivors with suspicious palpable nodules. Fine needle biopsy was performed to subjects with >10 mm nodules. The cumulative risk of secondary thyroid cancer was calculated by Kaplan-Meier method, and the effect of possible risk factors for the development of STC was calculated by Log-rank test.

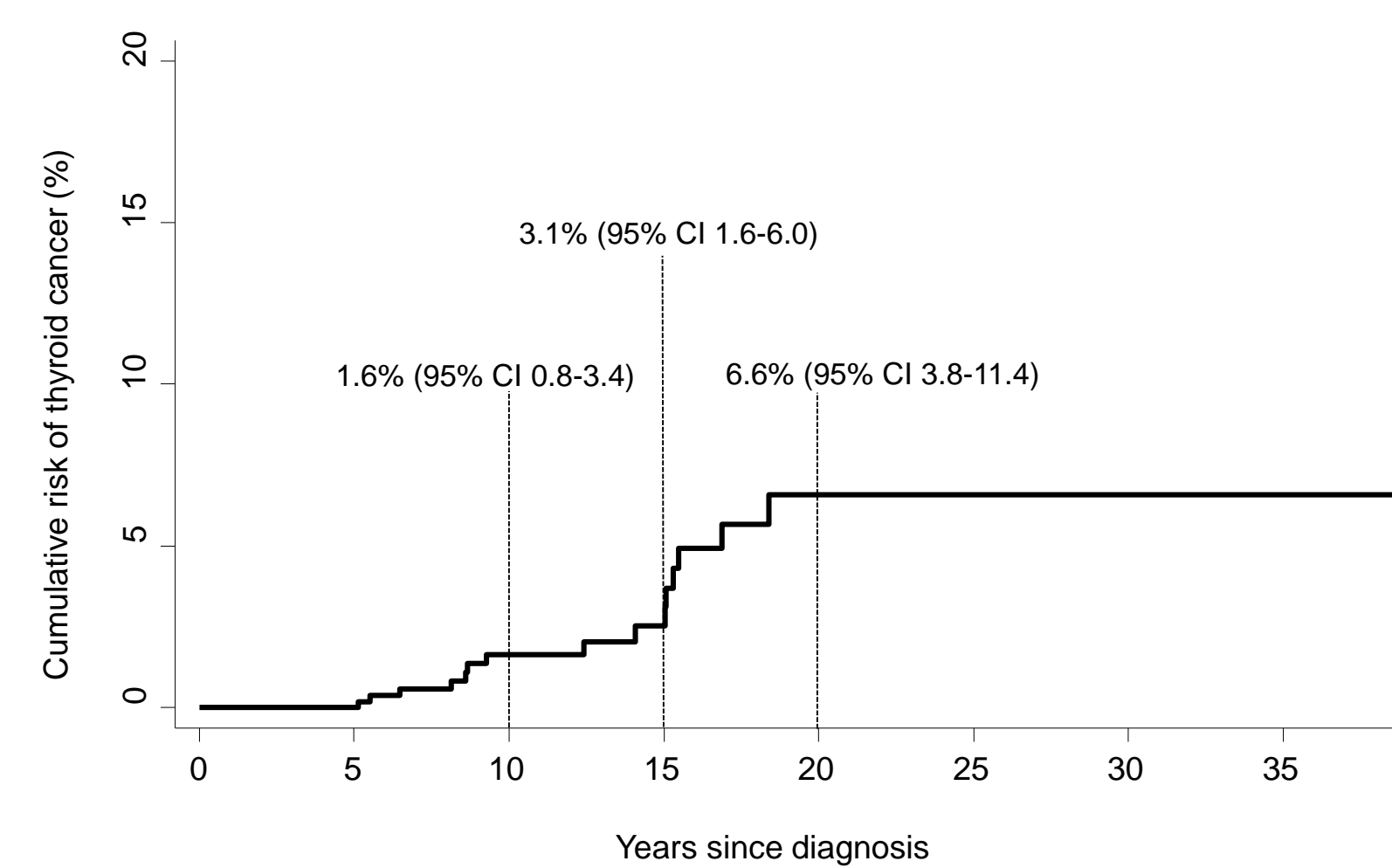
RESULTS:

632 (312 males; 49.4%) CCS with a median follow-up since diagnosis of 10.1 years (range 2.2-38.9) were evaluated. Of these, 147 (23.3%) received radiotherapy involving the thyroid, and 453 (71.7%) received alkylating agents (Table 1).

	CCS			P
	Total	without STC	with STC	
Gender, n (%)				
Male	312 (49.4)	301 (96.5)	11 (3.5)	
Female	320 (50.6)	316 (98.7)	4 (1.3)	
Median age at diagnosis, yrs (range)	4.3 (0 - 20.7)	4.3 (0 - 20.7)	8.5 (0.8 - 15.6)	0.058 [^]
Median follow-up, yrs (range)	10.1 (2.2 - 38.9)	10.1 (2.2-38.9)	12.4 (5.1-18.4)	0.629 [^]
Tumor diagnosis era, n (%)				0.002[§]
1975-1989	29 (4.6)	25 (86.2)	4 (13.8)	
1990-1999	158 (25.0)	152 (96.2)	6 (3.8)	
2000-2009	385 (60.9)	380 (98.7)	5 (1.3)	
≥2010	60 (9.5)	60 (100)	0	
Type of tumor, n (%)				0.849 [§]
Leukemia	177 (28.1)	171 (96.6)	6 (3.4)	
Lymphoma	94 (14.9)	91 (96.8)	3 (3.2)	
Neuroblastoma	126 (19.9)	123 (97.6)	3 (2.4)	
Sarcoma	83 (13.1)	82 (98.8)	1 (1.2)	
Wilms	47 (7.4)	47 (100)	0	
Other	105 (16.6)	103 (98.1)	2 (1.9)	
Radiotherapy involving thyroid, n (%)				<0.001[§]
No	485 (76.7)	482 (99.4)	3 (0.6)	
Yes	147 (23.3)	135 (91.8)	12 (8.2)	
>0-10 Gy	26 (17.7)	22 (84.6)	4 (15.4)	0.253 [§]
>10-20 Gy	84 (57.2)	77 (91.7)	7 (8.3)	
>20-30 Gy	13 (8.8)	12 (92.3)	1 (7.7)	
>30	24 (16.3)	24 (100)	0	
Alkylating agents, n (%)				1.000 [§]
No	179 (28.3)	175 (97.8)	4 (2.2)	
Yes	453 (71.7)	442 (97.6)	11 (2.4)	
CED (gr/m ²)				0.850 [§]
>0 - <8	240 (53.0)	234 (97.5)	6 (2.5)	
≥8 - <16	113 (24.9)	111 (98.2)	2 (1.8)	
≥16	100 (22.1)	97 (97.0)	3 (3.0)	
Total	632	617 (97.6)	15 (2.4)	

Pearson's chi-square test; [§]Fisher's exact test; [^]Mann-Whitney test

A total of 15 (2.4%) STC CCS were diagnosed between 5.1 and 18.4 years since first cancer diagnosis. Of these, 12 occurred among CCS irradiated to the thyroid area, while only 3 among those not irradiated. All were of the papillary sub-type.

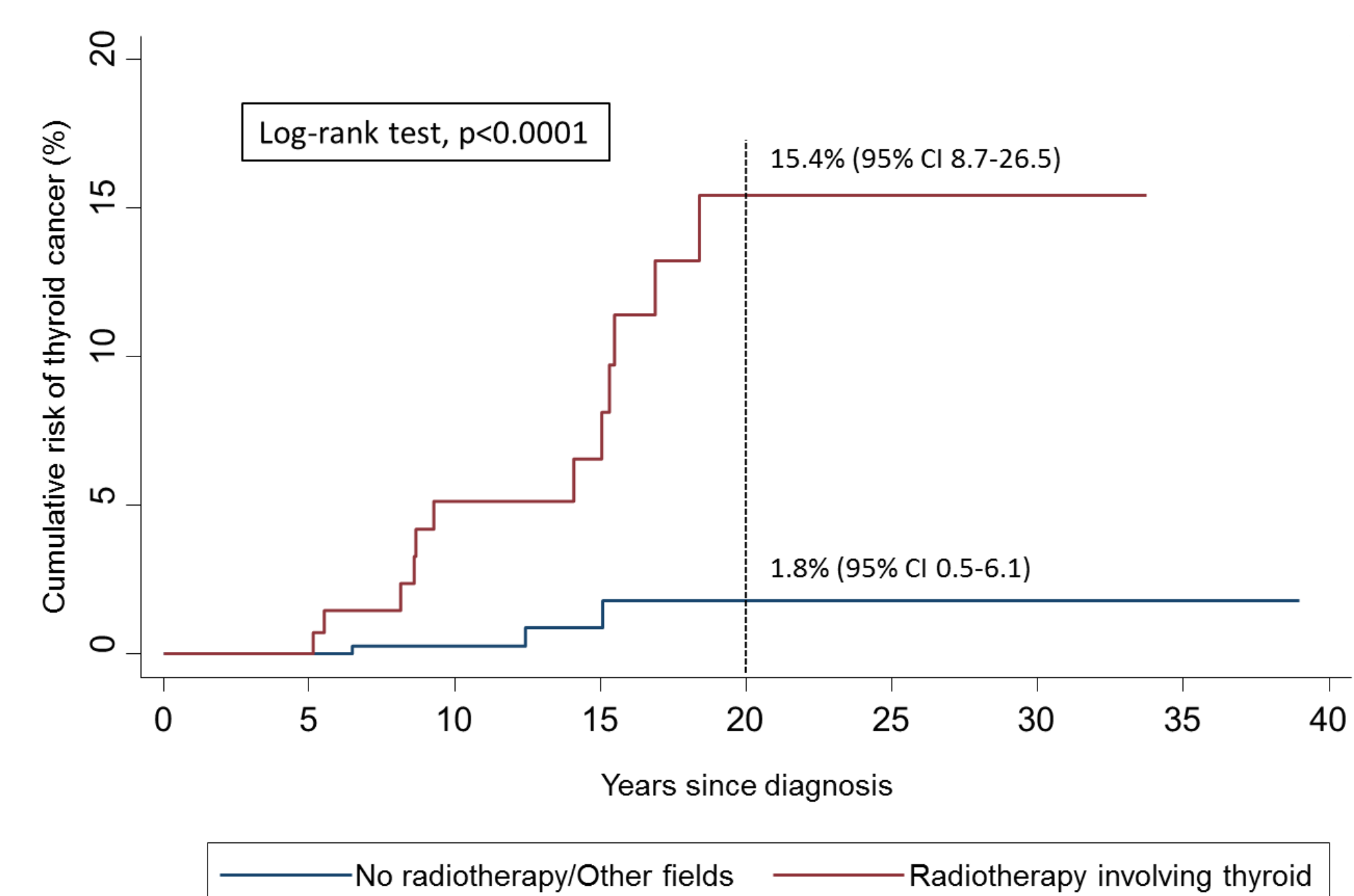


The overall cumulative risk of developing thyroid cancer at 10, 15, 20 years since diagnosis was 1.6 (95% CI 0.8-3.4), 3.1 (95% CI 1.6-6.0), and 6.6% (95% CI 3.8-11.4), respectively (Figure 1).

Analyzing the entire cohort, STC occurred in 8.2% of irradiated survivors and only in 0.6% of the not irradiated to the thyroid (p<0.001). Of the 3 cases occurring in this latter group, one subject was a female with Proteus syndrome previously treated for ovarian dysgerminoma; the 2nd case had a ganglioneuroma and the occurrence of STC lead to the genetic diagnosis of MEN2b syndrome; finally, the 3rd case was a Ewing sarcoma survivor for whom no genetic predisposition was documented.

Among irradiated survivors, an inverse correlation between dose of radiotherapy and risk of STC was observed, but the difference was not significant.

If the cumulative risk analysis was performed based on radiotherapy exposure, after 20 years since diagnosis, CCS irradiated to fields potentially involving the thyroid had a significantly higher cumulative risk of STC (15.4% 95% CI 8.7-26.5) as compared to those not irradiated or irradiated in other fields (1.8% 95% CI 0.5-6.1), p<0.0001. (Figure 2).



Treatment with alkylating agents was not associated with the risk of STC and there was also no effect based on CED.

CONCLUSIONS:

Long term active surveillance for STC is recommended for survivors previously exposed to radiotherapy potentially involving the thyroid. We also emphasize the necessity of further consensus on the most appropriate modality for thyroid cancer screening in CCS.

REFERENCES:

1 The Cyclophosphamide Equivalent Dose as an Approach for Quantifying Alkylating Agent Exposure. A Report from the Childhood Cancer Survivor Study Daniel M. Green, et al. *Pediatr Blood Cancer* 2015 Jan 1.