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ORIGINAL ARTICLE

Thyroid and parathyroid tumours in patients submitted to X-ray scalp epilation during the tinea capitis eradication campaign in the North of Portugal (1950–1963)

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Abstract Tinea capitis attained epidemical proportions in the fifth and sixth decades in Portugal, as in other countries. Before starting the utilization of griseofulvin in 1959, the best approach to treat tinea capitis infection was X-ray scalp epilation combined with topical antimycotic ointments. A long-term side effect of this therapy is thyroid disease, namely thyroid cancer; data on parathyroid lesions (hyperplasia, adenoma and carcinoma) are scarce. We observed clinically 1,375 individuals irradiated in childhood for tinea capitis treatment in the North of Portugal with the main purpose of evaluating thyroid and parathyroid tumours as possible sequelae of the irradiation treatment. For each individual, a cervical ultrasound and a serum calcium measurement were proposed. Fine needle aspiration cytology was suggested whenever ultrasound thyroid nodules presented suspicious features. We observed a 54 % frequency of thyroid nodules and a 2.8 % frequency of thyroid carcinoma (38/1,375). Nineteen of the 38 (50 %) carcinomas were diagnosed by us, whereas the remaining 19 carcinomas had been diagnosed and treated prior to our observation. The carcinomas were significantly more frequent in women than in men. Benign excised lesions were also significantly more frequent in women and in patients irradiated at younger ages. Seven women, considered asymptomatic until our clinical observation, had laboratory signs of hyperparathyroidism. The data we have obtained, namely high thyroid cancer frequency, corroborate previous data from childhood irradiated cohorts and highlight the need for the close follow-up of these populations in order to identify and treat early undiagnosed head and neck lesions. No evidence of increased parathyroid disease was found in this cohort of head and neck X-irradiated patients.

Keywords Tinea capitis · Thyroid · Parathyroid · Low-dose radiation · Scalp irradiation

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Introduction

Tinea capitis is a disease caused by several fungi species that infect the scalp, predominantly in children, being adult infection considered as exceptional [17, 52]. It attained epidemical proportions in the fifth and sixth decades in Portugal [13, 18], as in other countries [47], as there was no effective oral treatment and the disease was highly contagious. The cases were more frequent in population groups with poorer socio-economic conditions, but they also occurred in wealthy families [21]. Although there was no general survey, allowing to perform a solid evaluation of the diffusion and distribution of the disease [2], some estimations pointed to 10,000 to 50,000 affected scholar aged children in the North of Portugal [13, 20]. Considering that the disease attained the entire country, the number of infected children was certainly higher than the aforementioned, and these high figures explain the importance that tinea capitis infection represented for public health at that time.

The infection could be due to several fungi: *Trichophyton violaceum* was the most common agent [36] (60 % of the cases), *Trichophyton tonsurans* (14 %), *Microsporum canis* (10 %) and *Trichophyton schoenleinii* (15 %) [34]. The clinical expression and evolution of these infections led to the classification of the disease in two main types: tonsure tinea and non-tonsure tinea [29]. Tonsure tinea caused hair breaking by opposition to the non-tonsure tinea, in which the hair did not break usually [19]. Tonsure tinea was subdivided in trichophytic tinea and microsporic tinea. Trichophytic tinea was caused by several *Trichophyton* species and the microsporic tinea was caused mainly by *M. canis* [18, 22, 33]. The non-tonsure tinea (favus tinea) was caused by *T. schoenleinii* and was considered the worst form of tinea capitis disease [29] as it could trigger the onset of definitive alopecia [6, 17] (Fig. 1).

Before starting the utilization of griseofulvin in 1959 [16, 47], the oral antimycotic still in use today [24, 25], the best approach to tinea capitis treatment was X-ray scalp epilation combined with topical antimycotic ointments [14, 15, 17, 48, 47]; the X-ray epilation was considered as mandatory for the favus cases [11, 20, 22]. All over the world, thousands of children were submitted to this radiation intervention but the precise number is difficult to know as it was not a reportable disease [13, 48].

A few years after the irradiation treatment of tinea capitis had been stopped, the first studies about possible sequelae of the X-ray epilation were published [2, 3]. Since then, several other studies have shown an increase in thyroid cancer [31, 43, 41], skin cancer [8, 44, 46], meningioma [42] or permanent alopecia [6] amongst the irradiated individuals. Parathyroid tumours have been referred to be more frequent in the irradiation context [10, 53] but, as far as we know, for the tinea capitis irradiation setting, only one case report has been published [5]. Overall, such individuals are considered as a population at risk for head and neck neoplastic disease [48].

We had access to a cohort of individuals irradiated in childhood for tinea capitis treatment in the North of Portugal [7] and performed the clinical examination of 1,375 individuals between March 2006 and June 2012. The main purpose of the present study was to evaluate thyroid and parathyroid tumours as possible sequelae of the tinea capitis treatment.

Material and methods

Localization and contact of the irradiated individuals

We had access to the registry of a cohort of 5,356 individuals submitted, in childhood, to X-ray scalp epilation for tinea capitis treatment, in the former Dispensário Central de Higiene Social do Porto (DCHSP), between 1950 and 1963 [7]. As previously referred, the registry included name, address, age at irradiation treatment, irradiation dose and tinea capitis diagnosis (fungi classification) [7].

We undertook a huge effort to localize those individuals by searching their current addresses in several databases—telephone list, healthcare institutions databases and database for voter registration. The media (newspapers, radio and television) were used for repeatedly announcing the ongoing study. Once we had the current address, the individuals were contacted by a letter that provided a free phone number to contact us. A second letter was sent whenever the first one was not answered.

Clinical observation of the irradiated individuals

An initial examination was scheduled to every interested person between March 2006 and June 2012. This clinical observation was performed always by the same clinician (TG) using a protocol that included a thorough observation of the head and neck regions and the acquisition of a summarized clinical history. A cervical ultrasound was suggested to everyone without a previous history of total thyroidectomy, as well as a serum calcium measurement. The thyroid echo pattern was considered normal whenever no nodules or only nodules ≤5 mm were found. Nodules >5 mm were classified as thyroid nodules. The presence of poorly defined nodules was considered as thyroiditis. A fine needle aspiration biopsy (FNAB) was suggested to every individual presenting nodules larger than 15 mm and to the individuals presenting thyroid nodules smaller than 15 mm but with suspicious scan characteristics.

High calcium values, or in the upper limit of normal range, were suggested to be repeated. If the values kept high, a serum parathormone (PTH) measure and a determination of calcium in the 24 h urine were suggested.

Subsequent clinical observations were performed 4 years after the first observation and/or whenever the patients asked for it.

Statistical analysis

The PASW Statistics 19 program was used. Proportions were compared using X^2 test; comparison of the mean ages of the individuals at the irradiation procedure between the ones with pathology versus the ones without pathology was performed using the Student t test. A p value <0.05 was considered statistically significant with a 95 % confidence interval.

Results

Sample characterization

Figure 2 presents, in a diagram, the number of individuals enrolled in the study, participants, non-participants and individuals clinically observed during the study. From the 5,356 individuals of the original cohort, we were able to contact

Fig 1 **a** Trichophytic tinea. **b** Microsporic tinea. **c** Favus tinea. (Pictures gently provided by Prof. Aureliano da Fonseca)

3,797 individuals (or supposedly contact as we cannot be sure in the cases we did not get any answer) and 1,375 were clinically observed. Putting these 1,375 individuals together with the 442 deceased, those who are emigrants and those who refused to attend the clinical examination, 42 % (n= 2,223) of the cohort can be considered as traced. In total, the clinical observation and subsequent follow-up were made in 1,375 individuals (26 % of the original cohort).

The sample was constituted by 40 % men (n=546) and 60 % women (n=829), with a mean age at clinical examination of 58.6±4.4 and an age at irradiation of 7.2±3.0, without significant differences between men and women. Ninety four percent (94 %) received the standard radiation dose of 325–400 R (n=1,286), 6 % were subjected to two or three treatment sessions (applied whenever epilation was not obtained after the first treatment) and received ≥630 R (n=82). For seven individuals, there was no information on radiation dose.

When comparing to the original cohort, we have clinically examined more women and more individuals irradiated at younger age, being this difference significant (Table 1).

Thyroid pathology

At the clinical examination, we suggested that every individual (n=1,351 since 24 individuals had already been submitted to total thyroidectomy, 19 due to thyroid cancer) should be evaluated by ultrasonography.

We received 1,042 of the 1,351 ultrasounds we had suggested should be performed (77 %). Following the criteria mentioned in the previous section, 560 of the 1,042 ultrasounds presented nodules (54 %). The frequency of thyroid nodules was significantly associated with female gender (63 % of the women versus 40 % of the men, p<0.001); there was no significant association with age at irradiation or irradiation dose (Table 2). Based on the results of the ultrasounds, 270 FNABs were suggested following the criteria mentioned in the previous section. We obtained the FNAB reports from 171 of the 270 we had proposed (63 %).

Based on the 171 reports, 55 thyrodectomies were suggested; as far as we know 47 have been performed. In 19 cases, there was a diagnosis of thyroid cancer (see below), and in 28 cases, the diagnosis was benign lesions, nine follicular adenomas, 15 thyroid nodules and four cases in which the diagnosis was benign without having access to the histological report. Considering total benign excised lesions, this situation was more frequent in women as compared to men (7.1 versus 3.5 %, p=0.004) and also in patients irradiated at younger age (8.5 versus 4.4 %, p=0.002) (Table 2).

Considering the 1,375 participants, 38 presented thyroid cancer (2.8 %) and this neoplasia was significantly more common in women (3.5 % in women versus 1.6 % in men, p=0.04); there was no significant association with age at irradiation or irradiation dose (Table 2).

It was possible to review the histology from the surgically removed thyroids of 24 of the 38 X-irradiated patients with cancer; some of the thyroids presented more than one malignant lesion leading to a total of 36 carcinomas, the most common histotype being the follicular variant of papillary thyroid carcinoma (PTC), (20 out of 36 tumours—56 %) [9] (Fig. 3a). The other carcinomas were 14 classic PTC, one oncocytic variant of PTC and one follicular carcinoma [9]. The histological diagnoses of the 14 carcinomas in which we could not review the slides were seven cases of classic PTC (50 %) and seven cases of follicular variant of PTC (50 %). The histological subtypes were similar in the previously diagnosed patients (30.8 % of classic PTC and 69.2 % of follicular variant of PTC) and in those diagnosed by us (47.6 % of classic PTC and 52.4 % of follicular variant of PTC) (p=0.332).

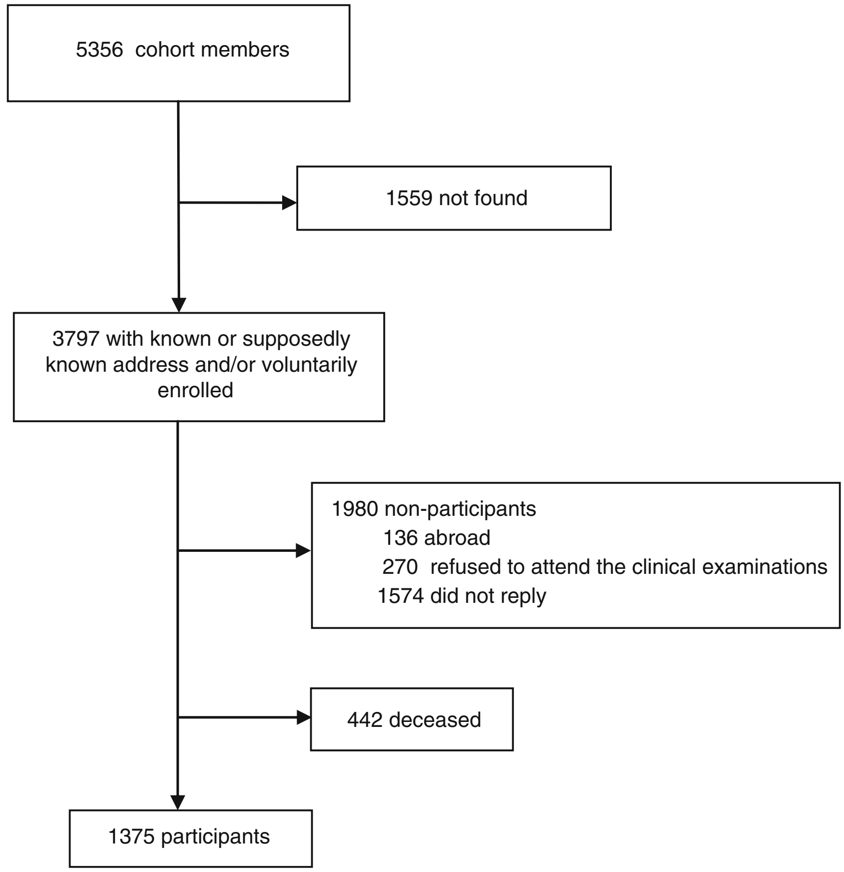
Out of 20 tumours of the follicular variant of PTC, 11 were diagnosed by us after ultrasound, FNAB and resection. In these 11 tumours, three had capsular invasion and none had vascular invasion. Of the remaining nine tumours, seven had capsular invasion and in one of them, there was also vascular invasion. Globally, the series was composed by tumours of low risk follicular variant of PTC.

There were 62 cases of thyroiditis (Table 2). Thyroiditis was significantly more frequent in women than in men (6.2 versus 2.0 %, respectively, p<0.001), and it was not significantly associated with age at irradiation or irradiation dose.

Parathyroid pathology

We received the reports of 970 of the 1,375 (71 %) individuals; we recommended the determination of calcium levels. Seventy-six individuals presented high or upper borderline calcium levels (6 %). In these cases, a repetition of the

Fig. 2 Flowchart depicting participants and non-participants from the cohort



measurement was recommended (Table 3). When the second measurement showed high calcium level or in upper borderline (n=23), further investigation was suggested through 24-h urine calcium and PTH serum measurements. Fourteen participants did this procedure and seven (0.5 %, 7/1,375), all women, were diagnosed with hyperparathyroidism and proposed to surgery. They were considered asymptomatic until our clinical observation, although most of them presented bone complaints. Six women were operated and had one parathyroid gland removed with primary hyperparathyroidism (PHPT) histologically confirmed (Fig. 3b); one woman refused surgery, although she had the disease confirmed by a parathyroid scintigraphy and was aware of the possible consequences of not removing the hyperplasic parathyroid gland. There were no previous diagnosed cases of PHPT in our sample.

Table 1 Comparison between cohort members and participants according to age at irradiation, gender and irradiation dose

	All cohort	Participants	p value
Age at irradiation [n (%)]			
≤5 years	1,358 (25)	449 (33)	<0.001
>5 years	3,946 (74)	926 (67)	
Not known	52 (1)	0	
Gender (n (%))			
Female	2,803 (52)	829 (60)	<0.001
Male	2,553 (48)	546 (40)	
Irradiation dose (n (%))			
325–400 R	5,022 (94)	1,286 (94)	0.957
≥630 R	318 (6)	82 (6)	
Not known	16 (<1)	7 (<1)	

Discussion

In our cohort of 1,375 individuals X-irradiated for tinea capitis treatment in childhood, there were 38 thyroid cancers representing a frequency of 2.8 %, a higher frequency than the 0.95 % reported in the tinea capitis Israeli cohort [43]. In this study [43], at variance with ours, the 0.95 % corresponded to data collection from health databases and without any clinical screening. In our series, if we consider only the thyroid cancers previously diagnosed, the rate of thyroid cancer drops to 1.4 %, a value that is closer to the irradiated population of the Israeli tinea capitis study.

The absence of a control group in our study turns very difficult, to evaluate the putative influence of irradiation on the frequency of thyroid cancer. In their study on the Israeli

Table 2 Thyroid lesions according to age at irradiation, gender and dose of irradiation

Sample characterization	Total	Nodules	Thyroid cancer	Thyroiditis	Excised benign lesion
Number of cases (*n* (%))	1,375	560/1,042 (53.7)	38/1,375 (2.8)	62/1,375 (4.5)	79/1,375 (5.7)
Age at irradiation					
≤5 years	449/1,375 (32.7)	187/326 (57.4)	16/449 (3.6)	27/449 (6.0)	38/449 (8.5)
>5 years	926/1,375 (67.3)	372/716 (52.0)	22/926 (2.4)	35/926 (3.8)	41/926 (4.4)
Gender (*n* (%))					
Female	829/1,375 (60.3)	392/626 (62.6)	29/829 (3.5)	51/829 (6.2)	60/829 (7.2)
Male	546/1,375 (39.7)	167/416 (40.1)	9/546 (1.6)	11/546 (2.0)	19/546 (3.5)
Irradiation dose (*n* (%))					
325–400 R	1,286/1,368 (94.0)	523/974 (53.7)	33/1,286 (2.6)	55/1,286 (4.3)	74/1,286 (5.8)
≥630 R	82/1,368 (6.0)	31/62 (50.0)	4/82 (4.9)	6/82 (7.3)	4/82 (4.9)

cohort, Sadetzki et al. [43] used non-irradiated siblings as controls and observed a frequency of thyroid cancer lower than that of the irradiated individuals (0.35 versus 0.95 %).

In Portugal, at variance with the USA in which a 1.1 % lifetime risk of developing thyroid cancer has been highlighted in the SEER database [32], there are no such data. In Japan, Suehiro [49] has shown a frequency of 0.44 % of thyroid cancer in a mass screening of non-irradiated individuals that attended a health centre over a period of 16 years. Also in Japan, a study on irradiated individuals (atomic bomb survivors), using a similar protocol to our own (thyroid ultrasonography), disclosed a 2.1 % frequency of thyroid cancer [27].

Considering the thousands of children submitted to tinea capitis in Portugal, we can expect a significant increase in thyroid cancer in such individuals, today aged 55–70, even with a small increase in thyroid cancer frequency due to the irradiation treatment, as pointed out by Shvarts et al. [47] in the Serbian tinea capitis campaign.

During the present study, we diagnosed 19 thyroid cancers, of which two cases of classic PTC had given rise to lymph

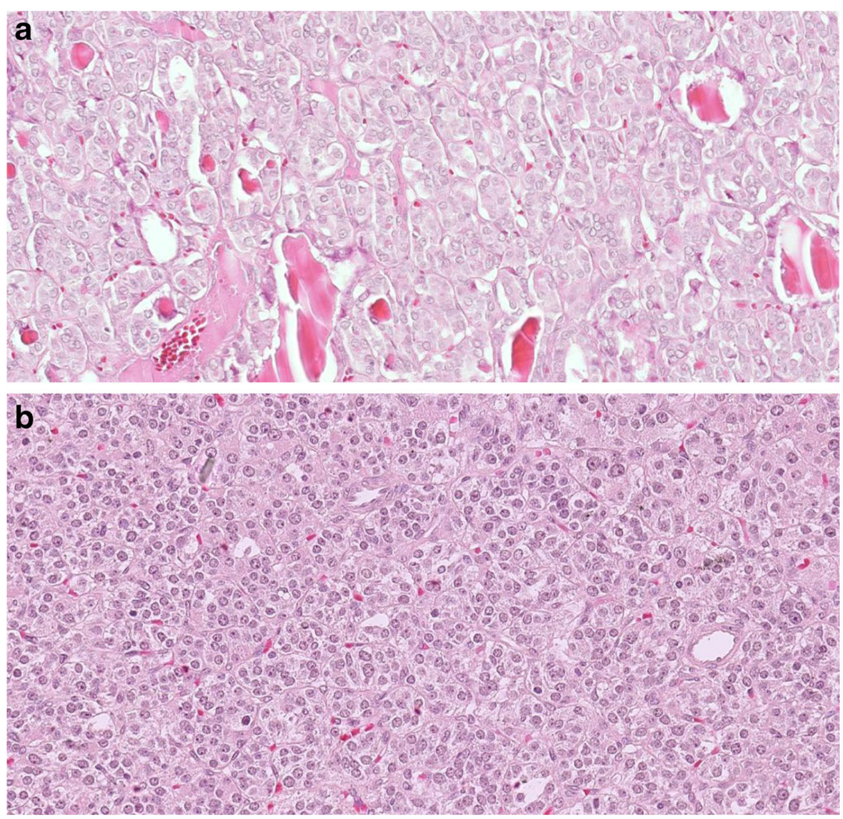


Fig. 3 **a** Follicular variant of papillary thyroid carcinoma. **b** Parathyroid adenoma (×200)

Table 3 Results of the calcium evaluation

Hypercalcaemia	76 (7.8 %)
Without information about calcium repetition	35 (3.6 %)
Calcium repeated	41 (4.2 %)
Second measurement normal	18 (1.8 %)
Second measurement high	23 (2.4 %)
PHPT hypothesis discarded after study	7 (0.7 %)
PHPT confirmed and surgically treated	6 (0.6 %)
Patient refused surgery	1 (0.1 %)
We do not have follow-up	9 (0.9 %)
Normal calcium level	894 (92.2 %)

node metastases, in asymptomatic individuals unaware of the cancer risk implications induced by the treatment they had been subjected to in childhood.

In our series, thyroid carcinoma, as well as other thyroid lesions, was significantly more frequent in women than in men. It is known that women are more prone to develop all sorts of thyroid pathology, and the additional risk of thyroid cancer due to radiation has been estimated to be 4–12 times higher in females than in males [40]. Thyroid carcinoma has also been described as significantly more frequent when the irradiation occurred in early childhood [39, 43, 51], but the difference regarding age found in our study was not statistically significant. Furthermore, we did not find enough evidence to advance a correlation between irradiation dose and thyroid cancer frequency in our series, probably due to the small number of individuals who received a high dose (6 %).

Thyroid nodules were observed in 54 % of the ultrasounds. The presence of a thyroid nodule is a common finding in thyroid ultrasound screenings, though usually with values lower than those observed in the present study (10–40 % in iodine sufficient areas, like Portugal [1, 4, 23, 38, 50]). The increased frequency of nodules found in our study may be attributable to the irradiation treatment [27, 30, 35]. This increased frequency becomes more important if we take into account that such nodules apparently have a higher risk of cancer development, as was the case in the atomic bomb survivors [26], suggesting the need for a careful observation of any irradiated individual with thyroid nodules.

Having had a benign lesion excised was significantly more frequent in patients irradiated at younger age. As we have clinically examined more patients irradiated at younger age in comparison to its percentage in the original cohort, we could have introduced a bias by recommending more surgeries than expected in a sporadic context. This seems not to be the case since if we consider only the surgeries performed before our clinical examination, this higher frequency of excised benign lesions in the patients irradiated at younger age kept statistically significant. As mentioned above, thyroid gland is most sensitive to early childhood irradiation [45].

We cannot discard once more the possibility that, in the present study, we may have got an overestimation of thyroid lesions. We have clinically observed more women as compared to the entire cohort (60 versus 52 %), and women are more prone to develop thyroid diseases, as previously discussed. On the other hand, a bias towards underestimation is also possible as we did not obtain information about the thyroid morphology of 23 % of the participants (315 cases without thyroid scans).

Hyperparathyroidism has been described as a possible late effect of childhood irradiation [12]. We diagnosed seven cases of PHPT in apparently asymptomatic women. The frequency found (0.5 %) was lower than the one reported in the general population (1.3 %) [37]. Here again, the situation may have been underestimated, as the diagnosis was done indirectly through serum calcium evaluation, that is not the best way to rule out the disease and, furthermore, we did not receive the calcium measurements from all the participants. As far as we know, only one study reporting a case of PHPT has been published in the tinea capitis irradiation setting [5]. Our results do not support the widespread belief that irradiation is a risk factor for parathyroid hyperplastic disease [10, 53]. It is possible that in other irradiated settings (atomic bomb survivors, head and neck cancer patients, acne patients, tonsillectomy patients), such risk is increased [28, 53], but it does not seem to be the case in the tinea capitis irradiation setting. Nevertheless, and taking in account the above mentioned limitations of our evaluation, we consider that a systematic assessment of this cohort through serum PTH measurements is advisable.

The results obtained in the present study corroborate and emphasize previous data concerning increased neoplastic thyroid risk in childhood irradiated cohorts, namely tinea capitis cohorts. The results we obtained also highlight the need for the close follow-up of irradiated populations in order to be able to identify as soon as possible and to treat the undiagnosed head and neck tumours that these individuals are at higher risk to develop. We believe that this represents an important public health problem considering the thousands of children that were submitted to scalp epilation for tinea capitis treatment.

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Conflict of interest We declare that we have no conflict of interest.

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