

Familial Differentiated Thyroid Carcinoma Shows Comparable Radioiodine Treatment Outcomes to Sporadic Disease under Standard Protocols

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Additional Declarations:

Tables are available in the Supplementary Files section.

Title page

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32

33 **Consent**

34 Consent has been obtained from each patient or subject after full explanation of the
35 purpose and nature of all procedures used. This analysis was approved by the ethics
36 review committee of our school (batch no. 2022-KY-022-02).

37

38 **Author contribution statement**

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40 (equal); Writing – review and editing (equal). Author 2: Data curation (equal);
41 Investigation (lead); Writing – original draft (equal); Writing – review and editing
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43 curation (supporting); Investigation (supporting). Author 5: Methodology (lead).
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50 **Abstract**

Background Existing studies suggest that familial differentiated thyroid carcinoma (FDTC) may exhibit greater aggressiveness and poorer prognosis compared to sporadic differentiated thyroid carcinoma (SDTC). However, there remains no clear consensus regarding specific clinicopathological manifestations of invasiveness and the necessity for additional therapeutic interventions in FDTC. Thus, we implemented a retrospective cohort study to compare FDTC and SDTC through comprehensive clinicopathological profiling and RAIT outcome.

Methods This retrospective cohort study compared 138 FDTC patients with 4816 SDTC controls through comprehensive clinicopathological profiling. Propensity score matching (PSM) was employed to assess the outcomes of radioiodine therapy (RAIT).

Results FDTC exhibited a higher incidence of tumor bilaterality (46.4% vs 38.0%, $P=0.047$) and the BRAF^{V600E} mutation rates (85.5% vs 78.0%, $P=0.046$), but lower frequencies of capsular, vascular, and lateral lymph node invasion. In FDTC, having >5 metastatic lymph nodes was an independent risk factor for RAIT outcomes (HR: 2.68, 95%CI: 1.10-6.52, $P=0.03$). While the family history was not correlated with RAIT efficacy ($P=0.154$), and overall disease-free survival (DFS) was comparable between FDTC and SDTC ($P=0.140$). Furthermore, FDTC families with ≥ 3 affected members exhibited larger metastatic lymph node diameters (1.1 cm vs 0.6 cm, $P=0.014$), higher lymph node burden (median 9 vs 4 nodes, $P=0.013$) and shorter DFS ($P=0.004$).

Conclusion FDTC presented unique biological behaviors, including increased bilaterality and the BRAF^{V600E} mutation, yet achieved comparable RAIT outcomes to SDTC under standard protocols. However, FDTC with ≥ 3 affected members showed higher aggressiveness and poor prognosis, which may warrant intensified management.

Keywords Familial Differentiated Thyroid Carcinoma; Radioiodine Treatment; Outcomes

Introduction

Thyroid cancer (TC) has emerged as the most prevalent endocrine malignancy globally, with differentiated thyroid carcinoma (DTC) constituting >90% of cases [1,2]. While most DTC cases are sporadic, 5%-15% occur in familial clusters defined as familial differentiated thyroid carcinoma (FDTC), which refers to the diagnosis of DTC in ≥ 2 first-degree relatives without radiation exposure history [3]. FDTC encompasses two subtypes: 1) syndromic FDTC associated with hereditary tumor syndromes characterized by distinct extra-thyroid manifestations, including familial adenomatous polyposis (FAP), Cowden syndrome among others [4,5]; 2) non-syndromic FDTC with isolated thyroid involvement, lacking syndromic features.

In recent years, studies have mainly focused on identifying novel mutations associated with non-syndromic FDTC, while relatively few studies regarding clinicopathological features and prognosis of FDTC have been published. Despite recognizing the aggressive potential of FDTC, consensus has not been reached on its specific clinicopathological signatures and the familial burden impact from the affected numbers. Also, no research has established a strict inclusion/exclusion cascade and systematically compared radioiodine therapy (RAIT) responsiveness between FDTC and sporadic differentiated thyroid cancer (SDTC) cohorts. The therapeutic implication of RAIT in FDTC is still unknown. In this study, we implemented a retrospective cohort study to compare FDTC and SDTC through comprehensive clinicopathological profiling. Furthermore, for the first time, we performed a rigorous analysis of RAIT outcomes using propensity score matching (PSM) methodology.

Materials and methods

Patients

In this retrospective analysis, we included 5151 DTC patients undergoing total/near-total thyroidectomy with radioiodine (I-131) examination or treatment during hospitalization from January 2016 to December 2022 at the Department of Nuclear Medicine, Zhujiang Hospital of Southern Medical University. Patients with incomplete records were excluded. In total, there were 138 (2.8%) FDTC patients coming from 114 kindreds and 4816 (97.2%) SDTC patients included in this study (Figure 1). The ratio of the actual hospitalizations to the total patients in kindreds was 59.2% (138/233). This analysis was approved by the ethics review committee of Zhujiang Hospital, Southern Medical University (batch no. 2022-KY-022-02).

Data collection

Patient's original data were collected and input into our electronic medical record system before RAIT, including demographics, records of the operation procedure, and the post-operation pathology report. Among them, capsular invasion refers to tumor cells penetrating the thyroid capsule; neural invasion refers to tumor cell involvement of nerve sheath structures. Both parameters are associated with increased locoregional aggressiveness and have been incorporated into ATA recurrence risk stratification and our institutional routine pathology reporting. All tissue specimens of primary lesions were initially evaluated by a qualified pathologist, followed by a secondary review by an experienced senior pathologist in our hospital. The family history of patients and their relatives was confirmed by patient interview and pathology report. In this study, FDTC was defined as the diagnosis of DTC in ≥ 2 first-degree relatives without a radiation exposure history. The information was also updated in the SDTC cohort during the follow-up survey to ensure no first-degree family member was diagnosed with TC until the end of this study (December 31, 2024). Tumor staging was according to the 8th edition of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual [6]

and recurrence risk stratification was based on the 2015 American Thyroid Association (ATA) guidelines [7]. A protocol of RAIT was established by our team to optimize the process of treatment [8,9].

Clinical-outcome evaluation

The follow-up time was defined as the duration between the initial thyroid operation and the final follow-up. Based on the 2015 ATA guidelines, the response of TC treatment could be divided into having a good response (ER), a biochemical incomplete response (BIR), a structural incomplete response (SIR), and an indeterminate response (IDR). The outcomes of RAIT were stratified into two groups in this research: long-term remission (ER and IDR) and persistent/recurrent (SIR and BIR). Persistent disease was defined as patients who remained at BIR or SIR from the time of initial surgery through the assessment of treatment response. Recurrent disease was defined as patients who achieved a good response after initial surgery but were subsequently assessed as BIR or SIR at a later follow up evaluation. The disease-free survival (DFS) was defined as the duration between the initial thyroid operation and the time when the disease persistent/recurrent was confirmed. Specific indicators referred to previous research conducted by our team [10].

Statistical analysis

Statistical analysis was conducted by SPSS version 27.0. Categorical variables were assessed with Pearson's chi-square tests and Fisher's exact test. Continuous variables were processed with the Mann-Whitney U test. The Kaplan-Meier curve was used to compare the DFS of patients receiving RAIT and was checked by the log-rank test. DFS curves were plotted using GraphPad Prism software version 9.0. The Cox proportional-hazards regression model was used for univariate and multivariate analysis to assess the

influencing factors of RAIT. PSM was used to conduct the survival analysis. $P<0.05$ indicates a statistically significant difference. In the post-hoc pairwise comparisons, $P<0.0167$ indicates a statistically significant difference.

Results

Clinicopathological comparisons of FDTC vs. SDTC

A total of 4953 patients were included in the study, and their demographic, clinical and pathological data are summarized in the Table1. FDTC was associated with a higher rate of bilateral lobe involvement (46.4% vs 38.0%, $P=0.047$) and a greater prevalence of the BRAF^{V600E} mutation (85.5% vs 78.0%, $P=0.046$) compared with SDTC. However, FDTC showed reduced invasiveness, with lower frequencies of capsular invasion (65.7% vs 74.1%, $P=0.023$) and vascular invasion (5.1% vs 12.1%, $P=0.013$). Furthermore, FDTC patients had a lower proportion (94.2% vs 98.6%, $P<0.001$) and smaller extent (central and lateral dissection: 44.9% vs 57.3%, $P=0.006$) to receive lymph node dissection. Accordingly, FDTC patients were more likely to present only central lymph node metastases as in N1a stage (43.8% vs 34.8%, $P=0.028$). The rest of the clinicopathological characteristics were not significantly associated with the presence of family history.

Clinicopathological comparisons of FDTC subgroups vs. SDTC

138 FDTC patients were included in the subgroup analysis of FDTC according to the number of affected family members. 128 patients (92.8%) had two affected members and 10 patients (7.2%) had three or more affected members in the family. Due to the limited sample size of patients with three or more affected members in the family, we merely describe the findings as observed and the relevant subgroup results should be interpreted with caution. The maximum diameter of metastatic lymph nodes appeared to be greater in those with three or more affected members (1.1 cm vs 0.6 cm, $P=0.014$) than

in those with two affected members. In the subgroup analysis of FDTC stratified by the generation of patients (Table 2), 78 patients (56.5%) were classified as first-generation onset and 60 (43.5%) as second-generation onset. Patients with second-generation onset tended to be younger at diagnosis than the first-generation cohort (33 years vs 44 years, $P<0.001$). The first-generation cohort seemed to show more tumor multifocality (70.1% vs. 56.4%, $P=0.016$) and a lower proportion of receiving lymph node dissection (98.6% vs. 93.6%, $P=0.006$) compared with the SDTC cohort. Finally, according to the relationship between the patient and their affected members, 68 patients (49.3%) were noted as parent/offspring type, 63 patients (45.7%) as sibling type, and 7 patients (5.0%) as parent/offspring/sibling type. No significant differences were observed between the three groups (Supplement Table 1).

Patient baseline characteristics in treatment efficacy studies

We investigated the influencing factors and outcomes of RAIT for FDTC and SDTC patients undergoing total/near-total thyroidectomy. The exclusion cascade was: 1) the presence of distant metastases; 2) the presence of metastatic structural lesions confirmed by imaging or biopsy before initial RAIT, or functional imaging-detected metastases proved by ^{131}I whole-body scan (WBS) following initial RAIT; 3) without receiving postoperative ^{131}I ablation; 4) <6 -month follow-up. Finally, 76 FDTC and 2309 SDTC patients met the eligibility of RAIT efficacy evaluation (Figure 2). In FDTC patients, 54 patients (71.1%) achieved long-term remission and 22 patients (28.9%) showed persistent/recurrent status. In SDTC patients, 1716 patients (74.3%) achieved long-term remission and 593 patients (25.7%) showed persistent/recurrent status. Up to the time of this study, the average follow-up duration of FDTC was 49 ± 31 months, with a median of 44 months. The average follow-up duration of SDTC was 41 ± 26 months, with a median of 36 months. FDTC exhibited higher stimulant thyroglobulin (ps-Tg) level

before RAIT compared to sporadic cases (median 4.7 vs 2.5 ng/ml, $P=0.011$) (Supplement Table 2). No significant differences were observed in the cumulative I-131 dose between familial and sporadic cohorts, nor across FDTC subgroups.

Influencing factors of RAIT in DTC

For FDTC patients, over five invaded lymph nodes ($HR: 2.68$, $95\%CI: 1.10-6.52$, $P=0.030$) was an independent risk factor for RAIT efficacy (Supplement Table 3), and FDTC patients who had over five invaded lymph nodes showed shorter DFS than the other group ($P=0.013$) (Figure 3A). In the preliminary data calculation of this study, the median number of cervical lymph node metastases among all DTC patients was found to be 5. For SDTC patients, the age over 55 ($P<0.001$), comorbidity with nodular goiter ($P=0.001$), multifocality ($P=0.038$), capsular invasion ($P=0.030$), vascular invasion ($P=0.001$), over five invaded lymph nodes ($P=0.010$), extracapsular extension of invaded lymph nodes ($P=0.012$), maximal diameter of metastatic lymph nodes ($P=0.014$) and the cumulative dose of I-131 ($P<0.001$) were independent risk factors for RAIT efficacy (Supplementary Table 4). SDTC patients who had over five invaded lymph nodes showed shorter DFS than the other group ($P<0.001$) (Figure 3B).

Comparisons of FDTC vs SDTC in RAIT outcomes

In order to explore the differences in RAIT outcomes between FDTC and SDTC, we conducted a 1:2 propensity score matching (PSM) between the two groups after adjusting variables like age, gender and all confounding factors examined in the above multivariable Cox analysis. After matching, all covariates showed p-values greater than 0.05, indicating balanced baseline characteristics between the two groups (Supplementary Table 5). Finally, a total of 189 DTC patients were enrolled, including 63 in the FDTC cohort and 126 in the SDTC cohort. No statistically significant difference was observed in RAIT outcomes between the two groups ($P=0.057$, long-term remission

of FDTC vs SDTC: 71.4% vs. 83.3%; persistent/recurrent: 28.6% vs 16.7%). Univariate and multivariate Cox regression analyses confirmed that family history was not significantly associated with RAIT efficacy in the matched cohort ($P=0.159$) (Table 3). Consistently, there was no statistically significant difference in DFS between the two groups ($P=0.140$) (Figure 3C).

Subgroup analysis was performed to further explore the differences in RAIT outcomes between FDTC and SDTC. It was observed that FDTC patients with three or more affected family members appeared to have relatively shorter DFS in comparison with those having two affected relatives ($P=0.010$) and SDTC patients ($P=0.001$) (Figure 3D). First-generation FDTC cases tended to show shorter DFS duration relative to second-generation FDTC patients ($P=0.004$) (Figure 3E), and seemingly presented less favorable DFS status than SDTC patients after 36 months of follow-up ($P=0.008$) (Figure 3E). Meanwhile, no obvious DFS divergence was noted among parent-offspring and sibling paired cases ($P=0.758$) (Figure 3F).

Discussion

Research on non-syndromic FDTC began with a report of 24-year-old identical twins with isolated familial DTC in 1955, published by Robinson and Orr [11]. Since then, several studies regarding having a family history of DTC have been published, suggesting FDTC is a unique clinical entity [12,13]. Nevertheless, studies on clinicopathological features of FDTC are controversial and limited. Moreover, evidence regarding RAIT outcomes in these patients is notably lacking.

In this study, we observed that FDTC may be more aggressive in certain clinicopathological. FDTC patients had a higher chance of bilateral lobes affected than SDTC patients. Capezzone et al. found that familial papillary thyroid carcinoma (FPTC) patients had bilateral tumors more frequently than sporadic papillary thyroid carcinoma

(SPTC) patients (39.6% vs 26.7%) [14]. The meta-analysis conducted by Wang et al. summarized that FDTC tended to have a higher risk of bilaterality (OR: 1.29, 95% CI: 1.00-1.66) based on four studies [15]. Furthermore, the analysis demonstrated that the rate of BRAF^{V600E} mutation was higher in FDTC compared with SDTC. Several studies have suggested that the BRAF^{V600E} mutation is a contributing factor to greater aggressiveness and poorer prognosis in PTC patients [16,17]. However, we also found that FDTC has a lower risk of lateral lymph node metastases. Accordingly, FDTC patients tended to receive less lymph node dissection than SDTC patients in surgical treatment, especially the operation of central and lateral lymph node dissection. It is worth mentioning that tumor bilaterality appears to be a risk factor for the development of lateral lymph node metastases [18], but this phenomenon has not been described in this study. Our study showed the age of diagnosis of the second generation was younger than the first generation and SDTC (33±8.5 vs 44±12.1 vs 40±12.7). Thus, the smaller range of lymph node metastases and dissection at diagnosis of FDTC might partly be owing to the early detection bias, which meant proactive screening in high-risk families promoted by DTC-affected family members.

However, earlier detection in screened families artificially lowers perceived aggressiveness but not aggressive biology. FDTC had a higher prevalence of bilateral lobes and the BRAF^{V600E} mutation, yet a lower frequency of vascular invasion. This observation was consistent with our previous finding [19] that PTC patients with the BRAF^{V600E} mutation are associated with a reduced incidence of vascular invasion. Thus, family history should be incorporated into the risk assessment for thyroid nodules.

The traditional definition of FDTC refers to the occurrence of two or more first-degree relatives simultaneously diagnosed with DTC, while a theoretical concern with this definition has been proposed as Charkes suggested that 62%-69% kindreds with only

two DTC-affected members may represent a contingent association of two sporadic cases according to his mathematical simulations. Therefore, only families with three or more affected relatives should be discussed as FDTC in terms of clinical and genetic patterns [20]. In this study, there was no difference in the rate of lymph node metastases between FDTC patients with three or more affected members and those with two affected members, which was consistent with other research [21]. However, the maximum diameter of metastatic lymph nodes was larger in FDTC patients with three or more affected members than in those with two affected members. Although it is worth noting that these results should be interpreted with caution due to the limited sample size, no previous studies have further explored the size of invaded lymph nodes, just focusing on the size of thyroid nodules. This finding provided preliminary insights for our further investigation into the characteristics of FDTC with three or more affected members. In a prospective cohort study with yearly screening of > 0.5 cm thyroid nodule(s) in individuals whose relatives were diagnosed with FDTC, the tumor was newly detected in 4.6% (2/43) individuals from families with two affected members, and in 22.7% (15/66) individuals from families with three or more patients affected ($P=0.010$) [19].

We reported a younger age at diagnosis in second-generation FDTC patients, but other clinicopathological features were similar between the first-generation and the second-generation, which is inconsistent with “genetic anticipation”. The concept refers to a phenomenon revealing a gradually earlier age and more aggressive features occurring with the diagnosis of genetic disorders in the next generation [22,23]. Moreover, Park et al. found that the second-generation showed a higher recurrence rate (50.0% vs. 19.0%) and shorter recurrence-free survival than the first-generation [24], but our study showed that the first-generation exhibited shorter DFS than the second-generation and the SDTC patients beyond 36 months. This difference could be owing to the age at diagnosis in our

study was lower than that of others. Capezzone et al. found that FPTC patients with age at diagnosis ≤ 45 years old had more aggressive tumor characteristics and showed worse outcome compared to the matched group of sporadic PTCs [25]. The mean age of the first-generation at the diagnosis in our study was 44 ± 12.1 years, and the mean age of other studies was more than 45 years. For example, the first-generation subgroup was associated with a higher risk of multifocality, although this trend was not found in overall FDTC patients [15,23,24,26–31]. Molecular genetic changes related to non-syndromic FDTC are complex and heterogeneous, involving polygenic inheritance patterns, which may explain the difference with “genetic anticipation”.

Intriguingly, our survival analysis showed that the long-term remission was not statistically significant between FDTC and SDTC. Capezzone et al. [14] suggested that FPTC patients had a higher rate of persistent disease at the time of the first follow-up (1–2 years after initial therapy), while the long-term clinical outcome was not different from SPTC. Several studies have come to similar conclusions in terms of final prognosis [23,27,32–34]. Some scholars have proposed that this phenomenon may be attributed to the generally favorable prognosis of DTC. Although radioiodine ablation was included as a factor in some studies, it has not been analyzed as a main part. In this study, we conducted PSM to adjust confounding factors and made strict inclusion criteria to exclude patients without receiving RAIT, patients with confirmed metastatic, enabling their RAIT efficacy to be comparable and evaluable. There are no significant differences in RAIT outcomes between FDTC and SDTC statistically. These findings suggest that standard surgical intervention may effectively mitigate the clinicopathologic aggressiveness of FDTC, yielding comparable therapeutic results to those in SDTC. Notably, the patient selection in the efficacy study may have introduced selection bias. The excluded patients may have included those with characteristics that prompted

physicians to alter treatment strategies based on the knowledge of a 'familial' thyroid tumor pattern.

However, the data showed a trend towards a lower long-term remission rate in the FDTC group (71.4%), thus close monitoring of FDTC patients remains essential. Furthermore, FDTC patients with three or more affected members had shorter DFS than those with two affected members, which lined up with our above conclusion that they had the larger maximum diameter of metastatic lymph nodes. Earlier studies have demonstrated that more and larger metastatic lymph nodes correspond with a higher likelihood of recurrence and a less favorable prognosis [35,36], and few studies found that FDTC with ≥ 3 first-degree affected relatives tended to have a poorer prognosis [13,37]. Additionally, the numerical difference in long-term remission between FDTC and SDTC is large (71.4% vs 83.3%), and the clinically relevant difference in RAIT outcomes might potentially be detected with larger cohorts. Thus, FDTC patients from families with three or more affected members may warrant a more proactive surgical approach and consideration of higher therapeutic ^{131}I doses. Additionally, non-DTC members in such high-risk families should undergo enhanced surveillance for early detection of thyroid cancer.

We examined the parameters impacting RAIT efficacy for FDTC. Having over five invaded lymph nodes was an independent risk factor, and those patients showed shorter DFS than the other group, which is consistent with the guidelines of 2015 ATA risk stratification that the number of over five metastatic lymph nodes was an important risk factor for recurrence [7]. Previous studies also showed that over five clinically apparent metastatic lymph nodes independently affected DFS in PTC patients and should be regarded as a high-risk caution [38]. It was also an important risk factor for RAIT outcomes in SDTC groups in our study.

This study has several limitations. Firstly, the prevalence of FDTC in our center was 2.8%, which is lower than the epidemiological data. Secondly, the number of FDTC and certain subgroups was a small sample size. This may have introduced selection bias, and the corresponding findings should therefore be regarded as exploratory and hypothesis-generating, necessitating validation in larger prospective studies. Furthermore, as Charkes noted, the occurrence of DTC in two family members may simply be a statistical coincidence [20]. This implies that if a true familial pattern with higher risk exists, this risk would be diluted by the large number of patients without such a familial pattern. Therefore, increasing the sample size of ≥ 3 affected members subgroup is necessary in future studies. Thirdly, some surgical data needed to be supplemented to more comprehensively evaluate the extent of cervical lymph node dissection in patients, as these factors may have an impact on DFS. Also, the study was limited by the inherent flaws of the single-center, retrospective study, and some patients belong to the same family, which may result in a lack of full independence in data selection. Finally, an extensive exploration of susceptibility genes and chromosomal regions associated with non-syndromic FDTC was awaited. Efforts to establish multi-center prospective studies with a larger-scale sample and a longer follow-up duration are underway.

Conclusion

FDTC displayed distinct biological features including increased bilaterality and a higher prevalence of BRAF V600E mutations, but under standard protocols, it may achieve RAIT outcomes comparable to those of SDTC. However, FDTC with ≥ 3 affected members showed a trend toward higher aggressiveness and poorer prognosis, raising the possibility that more intensive management might be beneficial in this

373 subgroup, though further validation is needed.

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Contribution statement

Author 1: Data curation (equal); Formal analysis (lead); Writing – original draft (equal); Writing – review and editing (equal). Author 2: Data curation (equal); Investigation (lead); Writing – original draft (equal); Writing – review and editing (equal). Author 3: Data curation (equal); Investigation (supporting). Author 4: Data curation (supporting); Investigation (supporting). Author 5: Methodology (lead). Author 6: Project administration (lead). Author 7: Conceptualization (equal); Supervision (equal). Author 8: Conceptualization (equal); Supervision (equal).

Conflict of Interest

The authors declare that they have no competing interests.

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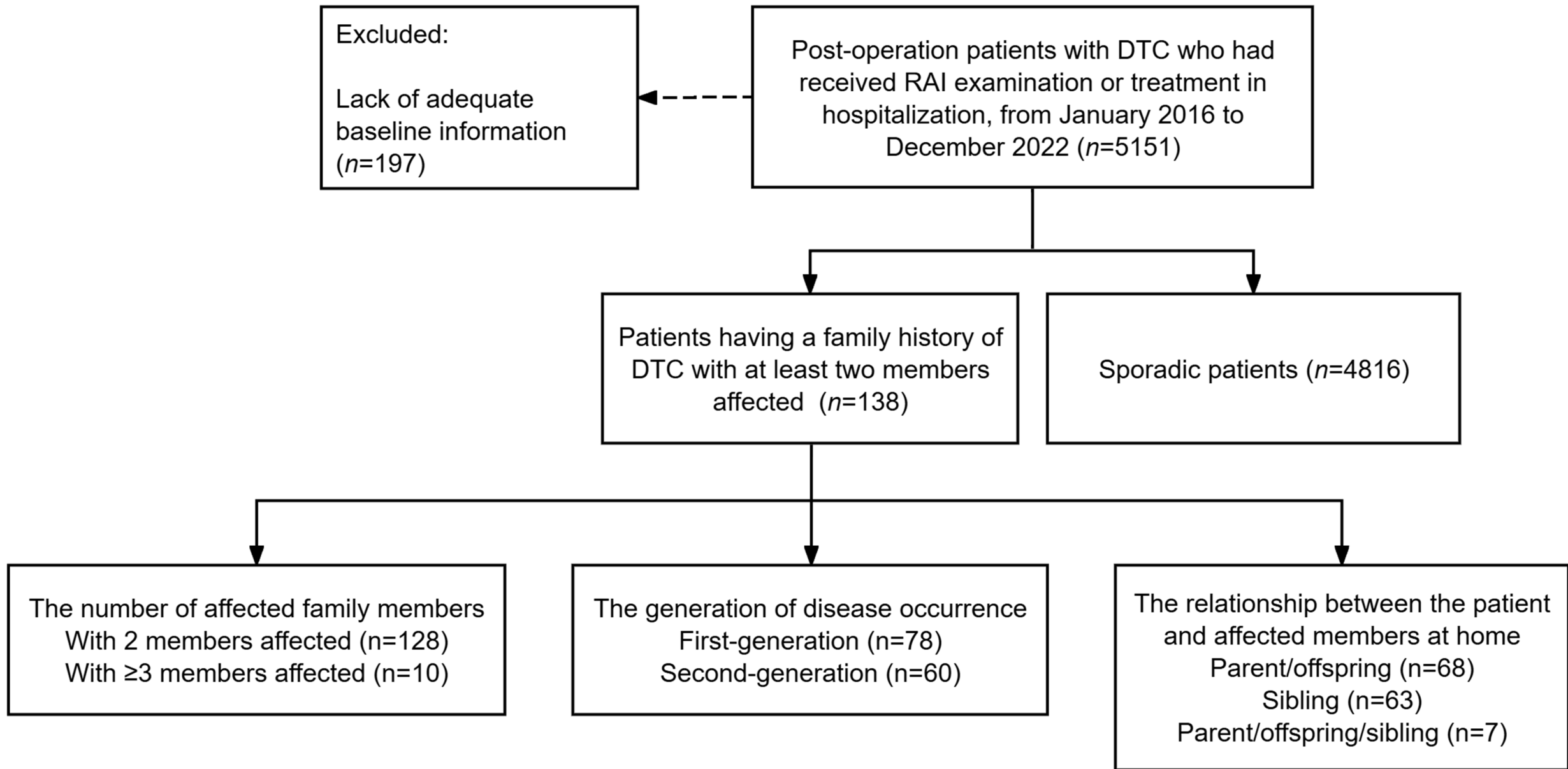
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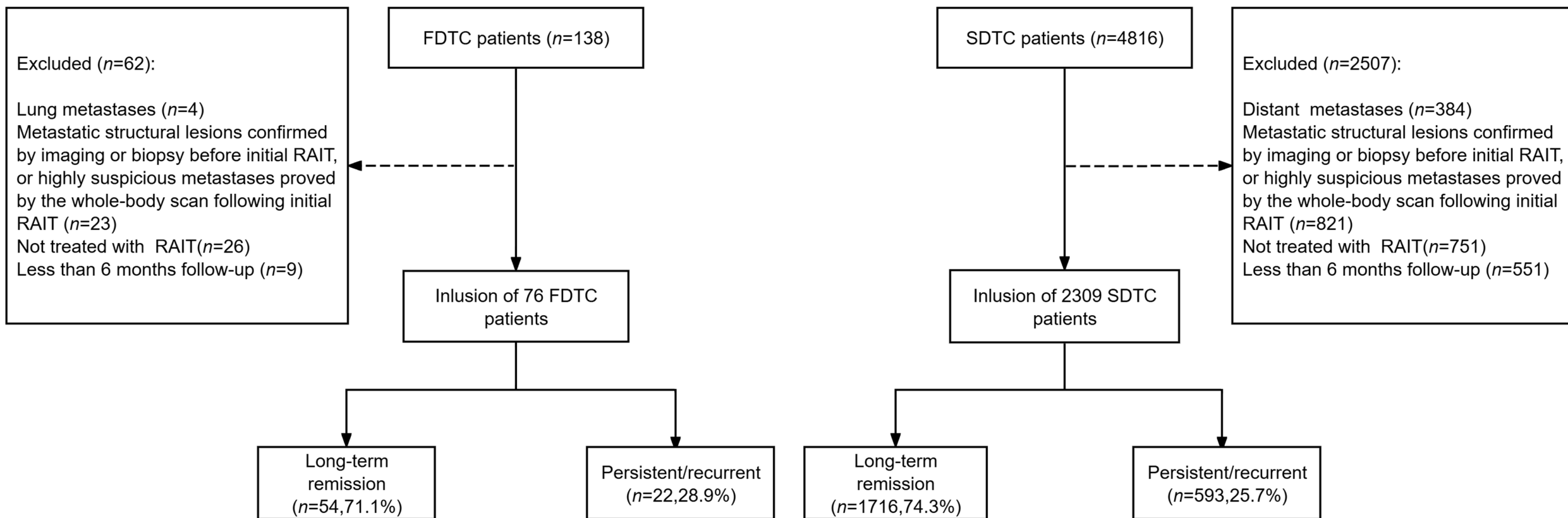
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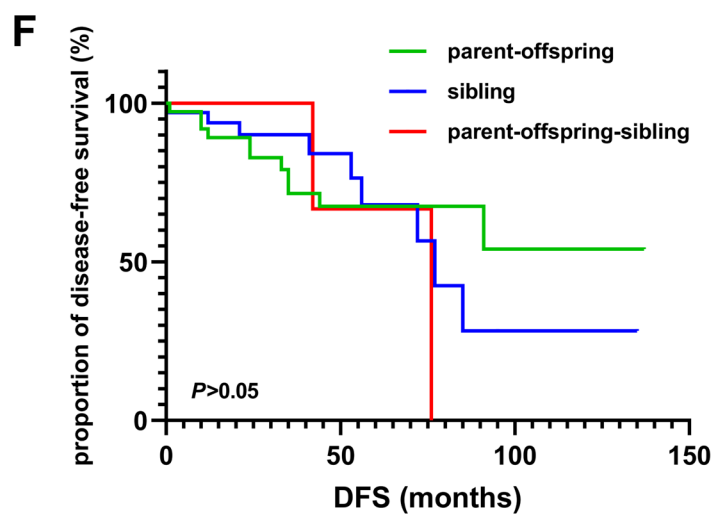
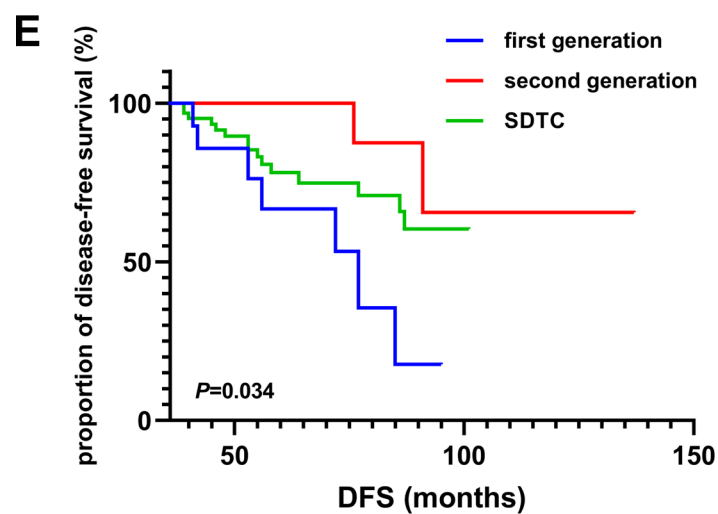
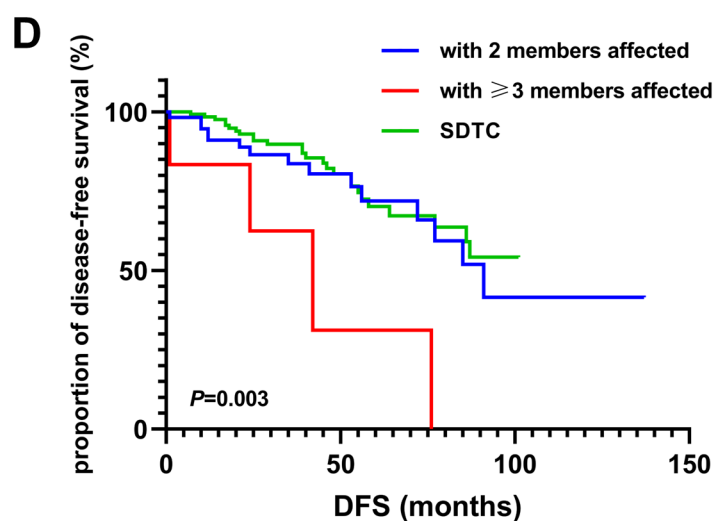
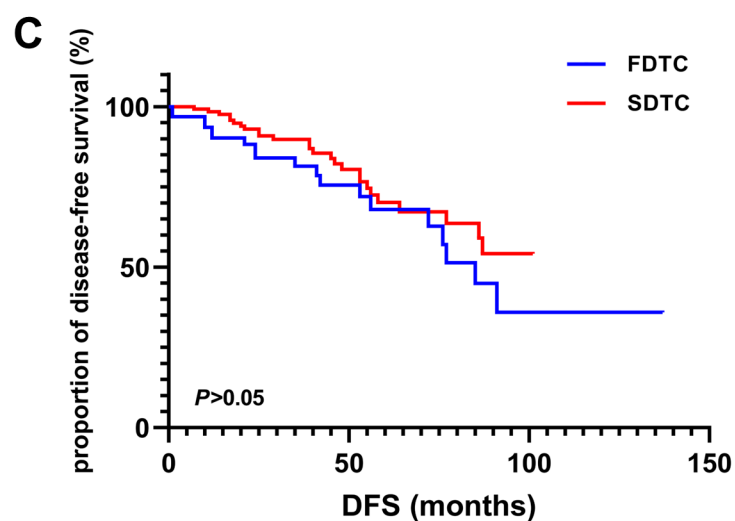
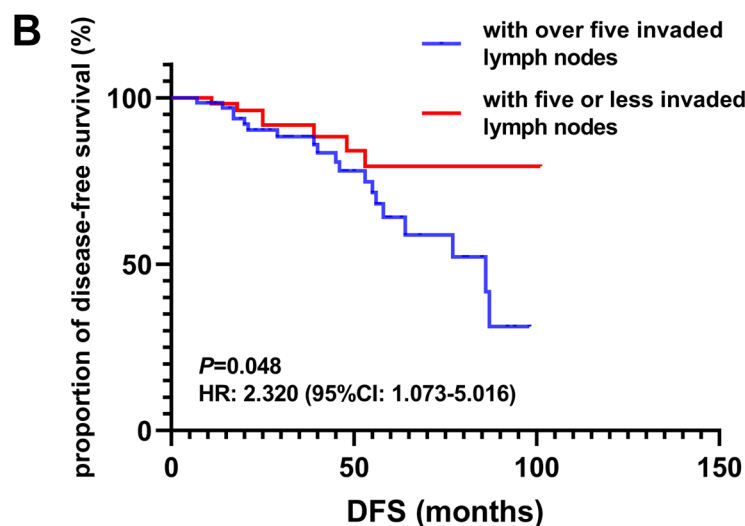
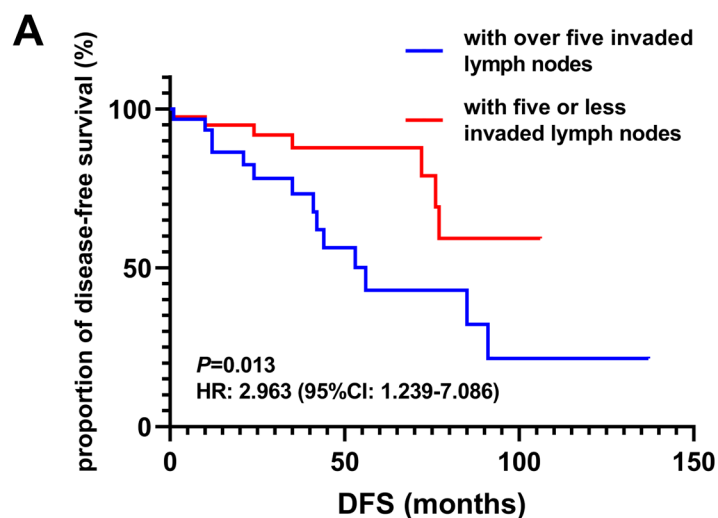
Figure 1. Flowchart of the inclusion/exclusion cascade and subgroup classification of FDTC patients. DTC: differentiated thyroid carcinoma; RAI: radioiodine.

Figure 2. Flowchart of the inclusion/exclusion cascade of DTC patients in the study of RAIT outcomes. FDTC: familial differentiated thyroid carcinoma; SDTC: sporadic differentiated thyroid carcinoma; RAIT: radioiodine therapy.

Figure 3. (A) DFS curves of FDTC with over five invaded lymph nodes and FDTC with five or less invaded lymph nodes ($P=0.013$). (B) DFS curves of FDTC and SDTC after propensity score matching ($P>0.05$). (C) DFS curves of FDTC with 2 members affected and FDTC with ≥ 3 members affected ($P=0.045$). (D) DFS curves of FDTC with 2 members affected, FDTC with ≥ 3 members affected and SDTC after propensity score matching ($P=0.003$). (E) DFS curves after 36 months of the first-generation FDTC, the second-generation FDTC and SDTC after propensity score matching ($P=0.034$). (F) DFS curves of the parent-offspring type FDTC, the sibling type FDTC and the parent-offspring-sibling type FDTC ($P>0.05$). DFS: disease-free survival; FDTC: familial differentiated thyroid carcinoma; SDTC: sporadic differentiated thyroid carcinoma; HR: hazard ratio; CI: confidence intervals.







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