Original Article

Synchronous papillary and follicular thyroid carcinomas: the first retrospective cohort study and literature review

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Background: Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) contribute to more than 95% of thyroid malignancies. However, synchronous PTC and FTC are less common; it is most commonly discovered incidentally as synchronous malignancies during operation, which adds difficulties to intraoperative decision-making and postoperative treatment. Therefore, we analyzed the clinicopathological characteristics and prognosis of patients with PTC and FTC in our center.

Methods: We conducted a search of single PTC, single FTC, and synchronous PTC/FTC patients who received initial surgery treatment at Fudan University Shanghai Cancer Center from 2006 to 2018 and collected paraffin-embedded samples of synchronous patients. Clinicopathological characteristics were collected from the electronic medical record system. Follow-up was performed through telephone contact or medical records. Exome sequencing was performed by ThyroLead panel.

Results: Total of 42 synchronous PTC/FTC patients, 244 single FTC patients, and 2,959 single PTC patients were included. It showed a similarity between the clinicopathological features of synchronous thyroid cancer patients and single PTC patients, with a greater proportion of females, higher probabilities of lymph node metastasis, and higher rate of concurrence of Hashimoto's disease. The disease-free survival (DFS) curve indicated a worse prognosis of the synchronous group and single PTC group compared to the single FTC group, who had a propensity for neck lymph node recurrence; however, logistic multivariate regression analysis did not find any factor related to recurrence in the synchronous group. After re-checking pathology, DNA extraction, and quality control, genetic alteration information of 62 samples including primary tumors and metastatic lymph nodes from 35 synchronous cancer patients was displayed. In total, 81 mutations and 1 fusion gene were identified, including mutations related to outcomes and targeted therapy. Besides, some rare mutations in thyroid cancer were found in these patients.

Conclusions: To conclude, synchronous PTC/FTC tend to be incidentally discovered during or after operation, behaving more like single PTC. The prognosis of synchronous patients is worse than that of single FTC patients and supplemental cervical lymph node dissection, total thyroidectomy, and postoperative radioiodine therapy should be taken into consideration after diagnosis. The next-generation sequencing (NGS) showed a unique molecular feature of synchronous patients with some rare mutations.

Keywords: Synchronous thyroid carcinoma; follicular thyroid carcinoma (FTC); papillary thyroid carcinoma (PTC); next-generation sequencing (NGS)

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Introduction

Thyroid cancer is the most common malignancy of the endocrine system, and is 5th common cancer in adult women worldwide (1). Papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC), defined as differentiated thyroid carcinoma (DTC), contribute more than 95% of thyroid cancer subtypes in the United States with a favorable prognosis (2,3).

However, synchronous PTC and FTC are rare and scarcely reported, with unclear clinicopathological characters and outcomes (4). Due to a lack of efficient means of preoperative diagnosis for FTC (5), these patients often undergo preoperative fine-needle aspiration (FNA) with cytology according to the Bethesda system for follicular neoplasm/suspicion of a follicular neoplasm (FN/SFN) or because ultrasound has indicated a single suspicious malignant nodule (6); intraoperative frozen section may also incidentally discover synchronous DTCs. The latest 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer did not mention this situation (3). In addition, the 5th edition of the World Health Organization (WHO) classification of thyroid cancer re-clustered subtypes of PTCs and emphasized the importance of molecular markers (7), which may deepen our understanding of the origin of thyroid tumors.

Due to the unfamiliarity with this complicated situation and lack of guidelines for the synchronous malignancies, surgeons faced with this incident have difficulties in making an optimal decision during surgical and postoperative intervention, and patients may not benefit from treatment to the greatest extent.

Here, we focused on the clinical features and genetic alteration of synchronous PTC and FTC cases, and compared the distinctions between the synchronous primary malignancies and single primary malignancy from our center. We present this article in accordance with the STROBE reporting checklist (available at https://tcr.amegroups.com/article/view/10.21037/tcr-23-1526/rc).

Highlight box

Key findings

- Synchronous papillary thyroid carcinoma (PTC) and follicular thyroid carcinoma (FTC) had higher rates of regional lymph node metastasis and concomitant Hashimoto's disease, and shorter disease-free survival (DFS) mainly due to short-term PTC recurrence compared to single FTC patients.

What is known and what is new?

- The guidelines for differentiated thyroid carcinoma are well established yet strategies for synchronous PTC and FTC are absent due to the rareness of this occasion.
- Although FTC size contributed to an advanced T stage, these synchronous cases had higher rates of regional lymph node metastasis and concomitant Hashimoto's disease, and shorter DFS mainly due to short-term PTC recurrence compared to single FTC patients.

What is the implication, and what should change now?

- Patients with synchronous PTC and FTC should receive treatment including cervical lymph node dissection, total thyroidectomy, and postoperative radioiodine therapy to reduce risk of recurrence.

Methods

Study cases and follow-up

We searched patients diagnosed with PTC, FTC, and synchronous PTC/FTC from 2006 to 2018 at Fudan University Shanghai Cancer Center, and found 45

synchronous PTC/FTC patients, 297 single FTC patients, and 4,458 single PTC patients in total. After follow-up, 42 synchronous cancer patients, 244 single FTC patients, and 2,959 single PTC patients were enrolled (3 patients with synchronous malignancies, 53 with single FTC, and 1,499 with single PTC did not undergo initial surgery in our center or were lost to follow-up). All of patients received initial surgical treatment and were diagnosed with synchronous PTC/FTC, single FTC, or single PTC through postoperative paraffin pathology. Tumors were staged and T stage of multifocal tumors (subdivided as "m") were determined by the largest tumor according to the 8th edition of American Joint Committee on Cancer (AJCC) staging system.

Patients were followed up through telephone contact or inpatient and outpatient medical records in our center. Recurrence was defined by fine-needle biopsy, imaging manifestation, or repeated surgery with confirmed pathology. Disease-free survival (DFS) was defined as the time from diagnosis to the first recurrence or the last contact.

Sample collection

We retrospectively searched surgical samples of those patients with synchronous thyroid carcinomas and then collected paraffin-embedded tumor samples including FTCs, PTCs, and metastatic lymph nodes at the Department of Pathology, Fudan University Shanghai Cancer Center.

Ethical statement

The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Fudan University Shanghai Cancer Center (No. 1612167-18). Written informed consent was provided by the patients to publish this paper.

DNA extraction and next-generation sequencing

DNA from paraffin-embedded tumor samples was isolated using the QIAamp DNA kit (QIAGEN, Hilden, Germany). In targeted next-generation sequencing (NGS) analysis, the ThyroLead panel (Topgen, Shanghai, China) covered 1,000 genes (BRAF, HRAS, KRAS, NRAS, RET, PIK3CA, CTNNB1, TP53, PTEN, IDH1, DICER1, MEN1, MTOR, TSHR, CDC73, and CDKN1B), and TERT promoter regions bp region and 4 coding exons and 12 introns (BRAF, NTRK1, RET, and PPARG) of frequently rearranged genes. Add at least 30 ng of genomic DNA and cut it using a Covaris E220 instrument (Covaris, Woburn, MA, USA). Sequence libraries were prepared using the KAPA HyperPlus Library Prep Kit (Roche, Basel, Switzerland) to first generate blunt-ended 5'-phosphorylated fragments. Add deoxyadenosine monophosphate (dAMP) to the 3' end (A-tailing) of double-stranded DNA (dsDNA) library fragments.

Next, attach the dsDNA adapter with 3'-dTMP to the A-tail library fragment. Library fragments with appropriate adapter sequences are amplified by ligation-mediated pre-capture polymerase chain reaction (PCR). Library capture was performed using an iGeneTech (Beijing, China) custom probe system, and the amplification product was biotinylated to capture sequences by using streptavidin-conjugated beads (Thermo Fisher, Waltham, MA, USA). Subsequently, pooled libraries containing captured DNA fragments were sequenced on an Illumina NextSeq 500 System (Illumina, San Diego, CA, USA) using the NextSeq 500/550 High Output Kit v2.5 (300 cycles) for 2×150 bp double-ended reads.

Data analysis

Illumina software bcl2fastq is used to generate FastQ files, and the number of mismatches is set to 1. The resulting FastQ files are processed by the software Fastp (https://github.com/OpenGene/fastp) to remove adapter sequences as well as poor quality readings (Phred scale quality below 15 for more than 40% of bases). The remaining reads were mapped to the hg19 reference genome using the BWA-MEM algorithm, and then sorted and duplicated labeled using SAMtools v1.9 (https://www.htslib.org/) and Picard v1.76 (https://broadinstitute.github.io/picard/), respectively. Next, the commercial software Sentieon TNseq (version 20180808; https://support.sentieon.com/) Short somatic variants are inferred using default parameters. Fusions were detected using the software GeneFuse (https://github.com/OpenGene/GeneFuse). All reported variants are manually checked on the Integrated Genomics Viewer (IGV) to ensure their reliability. ANNOVAR (2019Oct24; https://annovar.openbioinformatics.org/en/latest/) Single nucleotide variants (SNVs) and small insertions and deletions (InDels) for annotation reports. Since germline sequencing data was not available, we employed a rigorous

filtering strategy to remove potential germline variation. Variants with allele frequency (MAF) of ≥1% in 1 or more population databases (ESP, 1000Genome, ExAC, gnomAD) were excluded. Variants that are listed as "benign" in the ClinVar database (https://www.ncbi.nlm.nih.gov/clinvar/) are discarded.

Sequence variant confirmation is performed by conventional techniques, including Sanger sequencing and real-time polymerase reaction (rt-PCR). Analytical accuracy, limit of detection, and assay reproducibility were calculated using MedCalc statistical software version 9.6 (https://www.medcalc.org/). The waterfall plot of SNVs is plotted by the R package GenVisR.

Literature review

A systematic literature review was performed by searching relevant articles in PubMed, Embase, and Ovid. "Synchronous", "concomitant", "simultaneous", "DTC", "PTC", "FTC", and "thyroid carcinoma" were used as keywords. Cases with the following characteristics were collected: (I) synchronous PTC and FTC with definite diagnosis through pathology; (II) receiving initial surgery in the research.

Statistical analyses

Statistics analyses were performed using SPSS (version 20; https://www.ibm.com/support/pages/spss-statistics-220) and GraphPad Prism 7 (https://www.graphpad.com/support/prism-7-updates/). Contingency tables were used to correlate the synchronous tumors and single tumor with age, sex, tumor size, extrathyroidal extension, regional lymph node metastasis, distant metastasis, tumor-node-metastasis (TNM) stage, and Hashimoto's disease status. Nominal variables were analyzed by Pearson's chi-square test, chi-squared tests with continuity correction, or Fisher's exact test. DFS curves were drawn using Kaplan-Meier method. A 2-sided log-rank test was used for univariate analysis. A P value <0.05 was considered statistically significant.

Results

Incidental findings of synchronous DTC during or after operation

In the 42 cases of synchronous PTC and FTC, 6 patients went FNA preoperatively and 4 patients were diagnosed with PTC. In the 36 patients without preoperative FNA, 10 cases were considered benign nodules through ultrasonic manifestation [The American College of Radiology Thyroid Imaging Reporting and Data Systems (TI-RADS) level 3 or lower], 17 were suspicious for a single malignant nodule (TI-RADS level 4a or higher), and 8 patients were suspicious for multiple malignant nodules. From this, most synchronous malignancies were incidentally found during or after surgery.

Clinicopathological characteristics of synchronous and single malignancies

Clinicopathological information is shown in *Table 1*. Among 42 synchronous cases, 9 cases were male and 33 cases were female, in which the proportion of females was significantly higher than that in 244 single FTC cases (*Figure 1*). The gender ratio of the synchronous cohort was close to that of single PTC patients in our center. The median ages of the synchronous group, single PTC group, and single FTC group were 47, 44, and 46, respectively, and there was no difference in age among groups. In the synchronous group, tumor sizes of FTC were larger than those of PTC in 38 patients (not listed), indicating a predominant role of FTC in T stage of synchronous tumors. The regional lymph node metastasis rate was higher in the synchronous and single PTC group, mainly contributed by PTC metastasis. Among the 16 patients with regional lymph node metastasis in the synchronous group, 10 patients were revealed to have PTC metastasis whereas 6 patients were undefined (not listed in the table). There was no statistical significance among the three groups. Interestingly, the synchronous group showed the highest incidence of Hashimoto's disease, indicating that an inflammatory environment may contribute to synchronous malignancies in the thyroid.

Treatment modality of the synchronous group

All patients received initial surgical treatment in our center. Operation type and lymph node dissection were determined based on preoperative examination and intraoperative findings (*Table 2*). Among 42 cases with synchronous malignancies, 16 patients received lobectomy of the thyroid and 26 received total or near total thyroidectomy. Central lymph node dissection was routinely performed when malignancy was confirmed or suspicious. Of these 42 patients, 33 received central lymph node dissection

Table 1 Clinicopathological characteristics of patients

Variables	Single FTC (n=244)	Synchronous FTC and PTC (n=42)	Single PTC (n=2,959)
Sex, n (%)			
Male	97 (39.8)	9 (21.4)	767 (25.9)
Female	147 (60.2)	33 (78.6)	2,192 (74.1)
Age (years)			
Median	46	47	44
<55, n (%)	174 (71.3)	31 (73.8)	2,411 (81.5)
≥55, n (%)	70 (28.7)	11 (26.2)	548 (18.5)
Maximum of tumor diameter, n (%)			
<2 cm	76 (31.1)	23 (54.8)	2,566 (86.7)
2–4 cm	115 (47.1)	12 (28.6)	335 (11.3)
>4 cm	53 (21.7)	7 (16.7)	58 (2.0)
Extrathyroidal extension, n (%)			
+	12 (4.9)	3 (7.1)	279 (9.4)
–	232 (95.1)	39 (92.9)	2,680 (90.6)
Distant metastasis, n (%)			
+	12 (4.9)	0	21 (0.7)
–	232 (95.1)	42 (100.0)	2,938 (99.3)
Regional lymph node metastasis, n (%)			
+	9 (3.7)	16 (38.1)	1,562 (52.8)
–	235 (96.3)	26 (61.9)	1,397 (47.2)
AJCC stage, n (%)			
I	208 (85.2)	38 (90.5)	2,692 (91.0)
II	27 (11.1)	4 (9.5)	209 (7.1)
III & IV	9 (3.7)	0	58 (2.0)
Hashimoto disease, n (%)			
+	18 (7.4)	10 (23.8)	423 (14.3)
–	226 (92.6)	32 (76.2)	2,536 (85.7)

+, positive; –, negative; FTC, follicular thyroid carcinoma; PTC, papillary thyroid cancer; AJCC, American Joint Committee on Cancer.

and 10 received lateral lymph node dissection because of preoperative or intraoperative observation of suspicious metastasis of the lateral lymph node. A total of 11 patients received postoperative radioiodine therapy for adjuvant therapy.

Survival analysis and univariate analysis

We compared the DFS of 42 patients with synchronous malignancies, 229 single FTC patients, and 2,893 single PTC patients with matched TNM stage without distant metastasis (stage I/II with M_0). The median follow-up time was 70, 80, and 93 months for each group, respectively. Relapse occurred in 4 of 42 patients with synchronous malignancies within 15 months after initial surgery. PTC metastasis to lymph node was confirmed in 3 patients through repeated surgery and manifestation of lymph node recurrence was observed in 1 patient without pathological

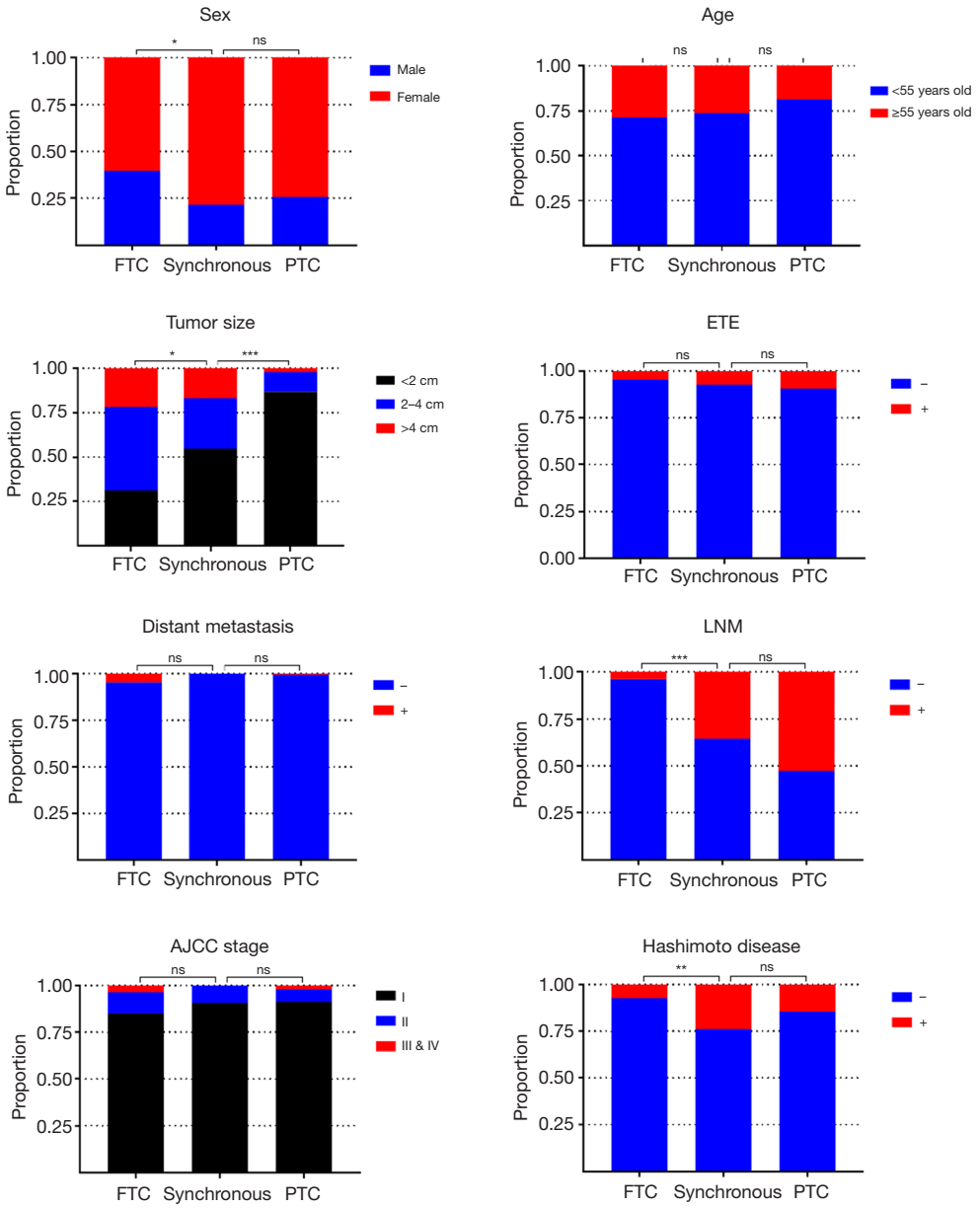

Figure 1 Clinicopathological features of synchronous, single PTC, and single FTC patients. +, positive; –, negative; ns, not significant; *, P<0.05; **, P<0.01; ***, P<0.001. PTC, papillary thyroid cancer; FTC, follicular thyroid carcinoma; ETE, extrathyroidal extension; LNM, lymph-node-metastases; AJCC, American Joint Committee on Cancer.

diagnosis. Survival analysis (*Figure 2*) showed a shorter DFS in the synchronous group than in the single FTC group (P<0.001), whereas no statistical significance was observed between the synchronous and PTC groups.

We performed univariate analysis including surgery type, lymph node dissection, and radioiodine therapy in the synchronous group (*Table 3*). All the factors showed no statistical significance [although the P value of central lymph node dissection was 0.03, its odds ratio (OR) range contained 1], which may result from the limited sample size and data distribution.

Mutational landscape of synchronous thyroid carcinomas by targeted sequencing

After searching, we collected 95 paraffin-embedded

Table 2 Treatment modality of synchronous cases

Variables	Number	Percentage
Surgery		
Lobectomy	16	38.1%
Total thyroidectomy or near total thyroidectomy	26	61.9%
Lymph node dissection		
Central lymph node dissection	32	76.2%
Lateral lymph node dissection	10	23.8%
Radioiodine therapy		
+	11	26.2%
–	31	73.8%

+, positive; –, negative.

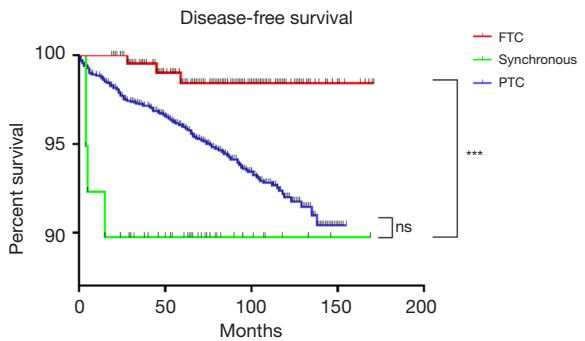

Figure 2 Disease-free survival of synchronous, single PTC, and single FTC patients. ns: not significant, ***, P<0.001. PTC, papillary thyroid cancer; FTC, follicular thyroid carcinoma.

samples of the synchronous group including PTC, FTC, and metastatic lymph node. DNA extraction and quality control were conducted, and 33 samples were subsequently excluded. Ultimately, 62 samples from 35 synchronous patients were analyzed.

Targeted NGS detected 81 mutations and 1 fusion gene in 32/35 patients (*Figure 3* and *Table 4*), BRAF mutation was the most common event in synchronous patients. In addition to V600E point, some rare mutations of BRAF including H608N and T599I were detected in PTC samples. Similar to a previous report (8), two BRAF K601E mutations were found in FTC samples.

TP53 and TERT promoter mutation were also detected in this cohort; however, correlation with prognosis was not found, which may on account of the limited sample size.

Literature review

After searching in databases, we found 13 relevant cases in total. The information of cases is presented in *Table 5*. More rarely, two patients had a simultaneous medullary thyroid carcinoma (MTC), and one patient had a simultaneous anaplastic thyroid carcinoma (ATC) and died 2 months after surgery of widespread distant metastasis.

Discussion

In this work, we performed the first cohort study of synchronous PTC and FTC. The clinicopathological characteristics of synchronous cases resembled PTC more than FTC. Compared to single FTC cases, synchronous cases had higher risk of relapse. However, the univariate analyses did not obtain statistical significance in surgery type, lymph node dissection, and radioiodine therapy.

The molecular features of synchronous thyroid carcinoma were demonstrated through NGS, showing a dependency to acquire rarer mutations. Therefore, it is unclear which factor contributes to a worse prognosis in synchronous patients as both a unique molecular landscape and a pathological type exist. In the future, a larger cohort study is required to manifest the underlying mechanism to poor outcome in the synchronous group.

Conclusions

The guidelines for DTC are well established yet strategies for synchronous PTC and FTC are absent due to the rareness of this occasion. In our study, 42 patients with synchronous PTC and FTC were enrolled. The existence of multiple primary malignancies was incidentally found in most cases. Although FTC size contributed to an advanced T stage, these synchronous cases had higher rates of regional lymph node metastasis and concomitant Hashimoto's disease, and shorter DFS mainly due to short-term PTC recurrence compared to single FTC patients. Although univariate analysis did not show significance, considering the worse outcome, it is necessary for patients with synchronous PTC and FTC to receive treatment including cervical lymph node dissection, total thyroidectomy, and postoperative radioiodine therapy to reduce risk of recurrence.

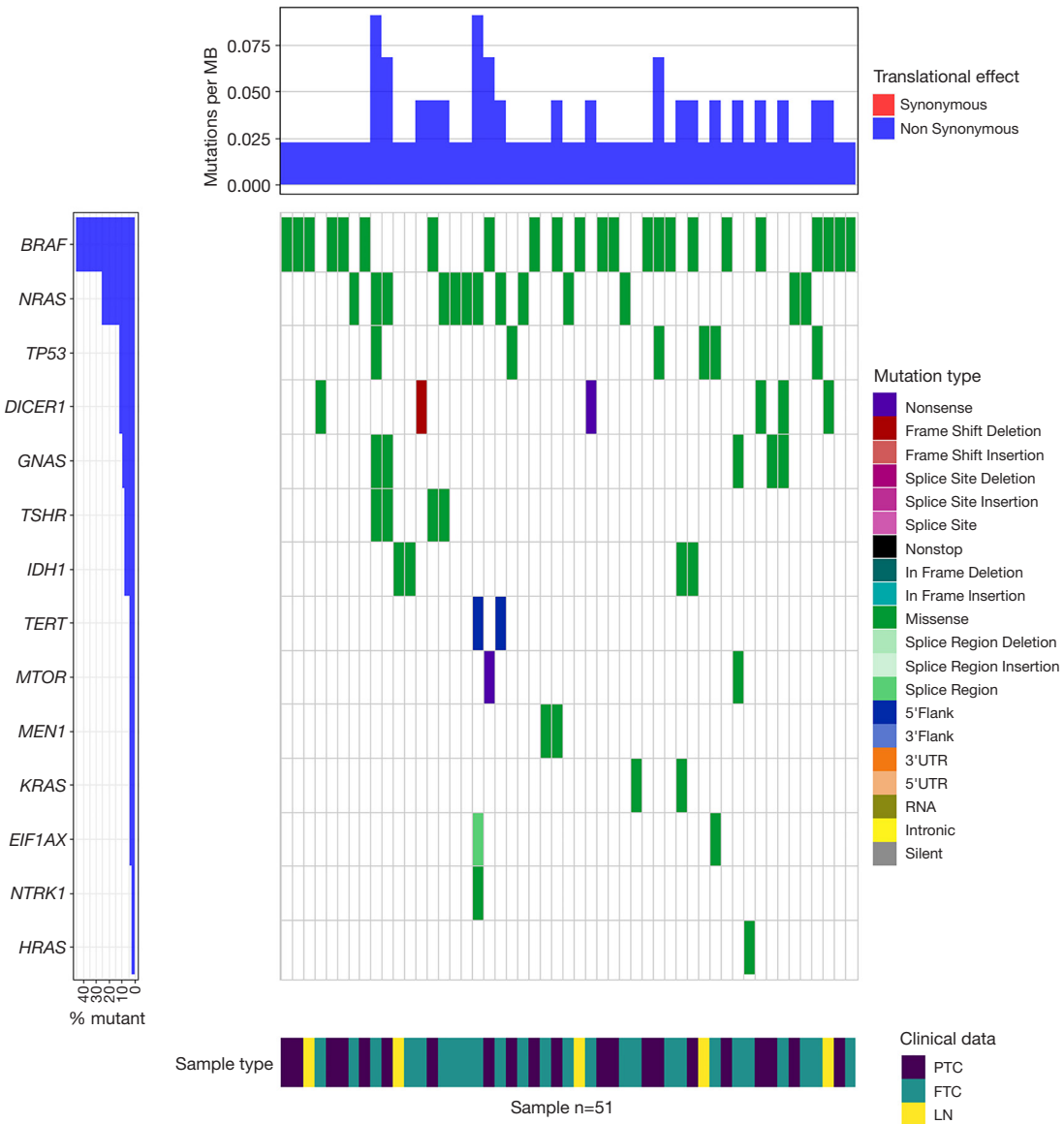

Figure 3 Mutation landscape of synchronous patients. PTC, papillary thyroid cancer; FTC, follicular thyroid carcinoma; LN, lymph node.

Table 3 Logistic regression analysis of risk factors associated with DFS

Factor	Surgical procedures	OR (95% CI)	P
Lateral lymph node dissection	–	1	0.52
	+	4.84 (0.524–44.717)	
Central lymph node dissection	–	1	0.03
	+	0.646 (0.038–10.938)	
Surgery	Lobectomy	1	0.09
	Total/near total thyroidectomy	1.021 (0.091–11.408)	
Radioiodine	–	1	0.99
	+	0 (0–not reach)	

+, positive; –, negative; DFS, disease-free survival; OR, odds ratio; CI, confidence interval.

Table 4 NGS results of synchronous patients

Mutation/gene fusion	Type of gene mutation	PTC, n	FTC, n	LN, n	Total, n
Mutations					
BRAF	BRAF Val600Glu	17	0	3	20
	BRAF Lys601Glu	0	2	0	2
	BRAF Thr599Ile	1	1	0	2
	BRAF His608Asn	1	0	0	1
NRAS	NRAS Gln61Lys	8	1	0	9
	NRAS Gln61Arg	6	1	0	7
TP53	TP53 Thr329Ile	0	1	1	2
	TP53 Arg267Gln	0	1	0	1
	TP53 Leu330Ile	1	0	0	1
	TP53 Arg379His	1	0	0	1
	TP53 Glu62Lys	0	1	0	1
DICER1	DICER1 Glu1813Gln	0	2	0	2
	DICER1 Glu1813Lys	1	0	0	1
	DICER1 Asp1810His	0	1	0	1
	DICER1 Asp1810Val	0	1	0	1
	DICER1 Ser117Ter	0	1	0	1
	DICER1 Met775Ile	0	0	1	1
	DICER1 c.3234_3237del	0	1	0	1
GNAS	GNAS Arg14His	1	1	0	2
	GNAS Ala40Val	1	1	0	2
	GNAS Arg26Cys	0	1	0	1
TSHR	TSHR Arg450Cys	1	1	0	2
	TSHR Lys751Arg	1	1	0	2
IDH1	IDH1 Ile154Leu	0	1	1	2
	IDH1 Met13Lys	1	1	0	2
KRAS	KRAS Gln61Arg	1	1	0	2
	KRAS c.180_181delinsAA	0	1	0	1
TERT	TERT C228T	0	2	0	2
MTOR	MTOR Gly1678Ter	1	0	0	1
	MTOR Val2389Ala	0	1	0	1
MEN1	MEN1 Arg176Gln	1	1	0	2
EIF1AX	EIF1AX Asn4Lys	0	1	0	1
	EIF1AX c.338-1_338delinsTA	0	1	0	1
NTRK	NTRK Pro619Ser	0	1	0	1
HRAS	HRAS Gln61Arg	0	1	0	1
Gene fusion					
CCDC6 exon1-RET exon11		0	0	1	1

NGS, next-generation sequencing; PTC, papillary thyroid cancer; FTC, follicular thyroid carcinoma; LN, lymph node.

Table 5 Systematic literature review of synchronous PTC and FTC

Patient	Age (years old)/gender	FTC (position and maximum of size)	PTC (position and maximum of size)	Cervical lymph node metastasis	Distant metastasis	Hashimoto disease	Surgery	Radioiodine therapy	Follow-up time	Outcome	Other disease
No. 1 (9)	31/female	Left lobe/ 1.3 cm	Left lobe/ 5 cm	–	–	+	Initial left lobectomy and additional total thyroidectomy	+	24 months	Complete remission	–
No. 2 (9)	61/male	Right lobe/ 6 cm	Right lobe/ 0.3 cm	Can not be assessed	–	+	Initial right lobectomy and additional thyroidectomy	+	15 months	Complete remission	–
No. 3 (9)	56/female	Left lobe/ 4.5 cm	Bilateral focus/1 cm	Can not be assessed	–	–	Total thyroidectomy	–	Lost	Lost	–
No. 4 (9)	35/female	Right/1.3 cm	Right/0.8 cm	–	–	–	Total thyroidectomy	–	Lost	Lost	–
No. 5 (9)	52/female	Right/2.7 cm	Right/0.8 cm	Can not be assessed	–	–	Total thyroidectomy	+	Not mentioned	Complete remission	–
No. 6 (9)	59/male	Left/5.0 cm	Left/1.5 cm	Can not be assessed	–	+	Total thyroidectomy	+	22 months	Complete remission	–
No. 7 (10)	64/female	Not mentioned	Not mentioned/ 1.7 cm	Not mentioned	Liver and brain (anaplastic thyroid carcinoma)	–	Total thyroidectomy	Chemotherapy	2 months	Dead	Anaplastic thyroid carcinoma
No. 8 (11)	72/male	Left lobe/ 2.5 cm	Right lobe/ 0.3 cm	Can not be assessed	–	–	Total thyroidectomy	+	48 months	Complete remission	Medullary thyroid carcinoma
No. 9 (12)	62/female	Left lobe/ 4.1 cm	Left lobe/ 1 cm	Can not be assessed	–	+	Initial left lobectomy and additional total thyroidectomy	+	Not mentioned	Not mentioned	–
No. 10 (13)	27/female	Right lobe/ 3 cm	Left lobe/not mentioned	Can not be assessed	–	–	Right lobectomy and isthmectomy	–	24 months	Complete remission	Medullary thyroid carcinoma
No. 11 (14)	64/male	Right lobe/ 4 cm	Bilateral focus/0.1 cm	Can not be assessed	–	–	Total thyroidectomy	+	24 months	Complete remission	–
No. 12 (14)	63/female	Right lobe/ 1.1 cm	Left lobe/ 1.7 cm	PTC metastasis	Rib, vertebra, liver and sacrum (FTC)	–	Total thyroidectomy	+	18 months	Alive with disease	–
No. 13 (15)	35/female	Right lobe/ 3 cm	Isthmus/ 0.6 cm	–	–	–	Total thyroidectomy	+	15 months	Complete remission	Clear cell carcinoma of kidney

+, positive; –, negative; PTC, papillary thyroid cancer; FTC, follicular thyroid carcinoma.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Medical Ethics Committee of Fudan University Shanghai Cancer Center (No. 1612167-18). Written informed consent was provided the patients to publish this paper.

References

1. Sung H, Ferlay J, Siegel RL, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin 2021;71:209-49.
2. Pereira M, Williams VL, Hallanger Johnson J, et al. Thyroid Cancer Incidence Trends in the United States: Association with Changes in Professional Guideline Recommendations. Thyroid 2020;30:1132-40.
3. Haugen BR, Alexander EK, Bible KC, et al. 2015 American Thyroid Association Management Guidelines for Adult Patients with Thyroid Nodules and Differentiated Thyroid Cancer: The American Thyroid Association Guidelines Task Force on Thyroid Nodules and Differentiated Thyroid Cancer. Thyroid 2016;26:1-133.
4. Cracolici V, Mujacic I, Kadri S, et al. Synchronous and Metastatic Papillary and Follicular Thyroid Carcinomas with Unique Molecular Signatures. Endocr Pathol 2018;29:9-14.
5. Grani G, Lamartina L, Durante C, et al. Follicular thyroid cancer and Hürthle cell carcinoma: challenges in diagnosis, treatment, and clinical management. Lancet Diabetes Endocrinol 2018;6:500-14.
6. Cibas ES, Ali SZ. The 2017 Bethesda System for Reporting Thyroid Cytopathology. Thyroid 2017;27:1341-6.
7. Baloch ZW, Asa SL, Barletta JA, et al. Overview of the 2022 WHO Classification of Thyroid Neoplasms. Endocr Pathol 2022;33:27-63.
8. Afkhami M, Karunamurthy A, Chiosea S, et al. Histopathologic and Clinical Characterization of Thyroid Tumors Carrying the BRAF(K601E) Mutation. Thyroid 2016;26:242-7.
9. Abdelaal A, El Ansari W, Abusabeib A, et al. Simultaneous occurrence of follicular and papillary thyroid carcinomas in same thyroid lobe: A case series of six patients from Qatar. Int J Surg Case Rep 2020;73:65-70.
10. Ganguly R, Mitra S, Datta AK. Synchronous occurrence of anaplastic, follicular and papillary carcinomas with follicular adenoma in thyroid gland. Indian J Pathol Microbiol 2010;53:337-9.
11. Mazeh H, Orlev A, Mizrahi I, et al. Concurrent Medullary, Papillary, and Follicular Thyroid Carcinomas

and Simultaneous Cushing's Syndrome. Eur Thyroid J 2015;4:65-8.
12. Plauche V, Dewenter T, Walvekar RR. Follicular and papillary carcinoma: a thyroid collision tumor. Indian J Otolaryngol Head Neck Surg 2013;65:182-4.
13. González-Cámpora R, Lopez-Garrido J, Martin-Lacave I, et al. Concurrence of a symptomatic encapsulated follicular carcinoma, an occult papillary carcinoma and a medullary carcinoma in the same patient. Histopathology 1992;21:380-2.
14. Verdi D, Pennelli G, Galuppini F, et al. Synchronous medullary, papillary and follicular carcinomas in the same thyroid: case report and review of literature. Updates Surg 2013;65:329-32.
15. Ma J, Du J, Zhang Z, et al. Synchronous primary triple carcinoma of thyroid and kidney accompanied by solitary fibrous tumor of the kidney: a unique case report. Int J Clin Exp Pathol 2014;7:4268-73.

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