Original Article

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Retrospective Analysis of Patients with Synchronous Primary Breast and Thyroid Carcinoma

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ABSTRACT

Objective: Breast and thyroid cancers are commonly encountered malignancies. Increased risk of breast cancer in follow-up period of thyroid cancer or vice versa has been reported. However, they have some associations, synchronous presentation of these tumors is rare. We presented 12 patients diagnosed as breast and thyroid cancer and treated at the same time.

Materials and Methods: Mastectomy and thyroidectomy were performed in 19 patients at the same time. 7 patients were excluded because of benign thyroid pathology. Therefore 12 patients who had diagnosis of synchronous breast and thyroid cancer were included. Data regarding clinical, pathological, treatment and prognostic factors was retrospectively analyzed.

Results: Total thyroidectomy was performed in all patients. The mean age of patients was 54 years (min. 44- max. 70). Only one patient was male. Thyroid pathology was detected preoperatively by FDG PET-CT scan in 11 patients. Breast reconstruction was performed in three patients. The most commonly seen thyroid malignancy was papillary thyroid carcinoma. Postoperative complication rate was 33.3%. Adjuvant chemotherapy was given in 11 patients whereas one patient received adjuvant radiotherapy.

Conclusion: Although synchronous presentation of breast and thyroid cancer is rare, surgical treatment of both of these tumors can be safely performed at the same time. Association of these tumors should be evaluated by large scaled studies.

Keywords: Breast cancer, thyroid cancer, synchronous cancer, mastectomy, thyroidectomy

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Introduction

Breast cancer is the most common cancer in women and it is the second most common cause of death among women due to cancer (1, 2). However, thyroid cancer is projected to be higher than lung, colorectal, and ovarian cancers in near future and estimated to be the third most common cancer of women in USA; it has not been a common cause of death due to cancer (3). 5-year survival rate of thyroid cancer ranges between 95-97% and 5-year survival rate of women with breast cancer is reported 81.9% therefore breast cancer is the determinant for survival in a patient with both breast and thyroid cancer (4, 5).

Both breast and thyroid cancers are frequent among women than men and they both have peak incidence in postmenopausal period (2). This finding, may be coincidence, has lead authors to investigate the association between breast and thyroid cancers. It is believed that they both have some interactions in hormonal and genetic level (6). Increased risk for second primary malignancies after diagnosis of thyroid carcinoma such as salivary gland, small intestine and adrenal gland has been found and this risk increases for breast cancer as the duration of the follow-up is prolonged (7). Although genetic factors, hormones and irradiation have been regarded as risk factors, no absolute relationship has been established yet between them. Either in breast cancer survivors, especially when HER-2 receptor was positive, or in thyroid cancer survivors, increased risk of the other cancer has been found (7, 8). This topic has been investigated by cohort and case-control studies in survivors butfew studies presented patients diagnosed synchronously and treated at the same time (9, 10).

In this study, we present patients who were diagnosed preoperatively as synchronous breast cancer and thyroid pathology and underwent mastectomy and thyroidectomy at the same session.

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Materials and Methods

In total, 1297 thyroidectomies and 1210 mastectomies were performed between November 2011 and January 2016 at our institute. Data of patients were retrospectively collected via patient records. Among these patients, both mastectomy and thyroidectomy were performed in 19 patients. A total of 729 patients with diagnosis of thyroid cancer and 579 patients with diagnosis of breast cancer were found. 12 patients had diagnosis of synchronous breast and thyroid cancer, whereas 7 patients had breast cancer and benign thyroid disease.

Characteristics of patients, pathological characteristics of both cancers, neoadjuvant or adjuvant chemoradiotherapy status, postoperative radioiodine ablation therapy status, postoperative complications, recurrence, survival, disease-free survival and follow-up of the patients are given in Table 1 and 2. This study was conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional or regional) and with the Helsinki Declaration.

Statistical Packages for the Social Sciences (SPSS) software package was used for statistical analysis version 17.0 (SPSS Inc., Chicago, IL, USA). If continuous variables were normal, they were described as the mean±standard deviation ($p>0.05$ in Kolmogorov-Smirnov test or Shapira-Wilk ($n<30$)), and if the continuous variables were not normal, they were described as the median.

Results

A total of 12 mastectomies and thyroidectomies were performed simultaneouly in patients with preoperative diagnosis of breast cancer and thyroid pathology. Mean age of patients was 54 years (min. 44-max. 70). Only 1 (8.3%) patient was male. Half of the patients had preoperative thyroid fine needle aspiration with diagnosis of 3 malignant cytology, 2 Hurthle cell neoplasia and 1 follicular neoplasia. Other 6 patients had either hyperthyroidism or thyroid nodule larger than 3 cm. on physical examination and ultrasound.

11 (91.7%) patients had preoperative FDG PET-CT scan and thyroid pathology was detected in all of them. In all 12 patients, primary complaint of the patient was lump or swelling in the breast therefore none of the patients presented with primary thyroid pathology. Thyroid patholgy was detected on FDG PET-CT scan or physical examination. Total thyroidectomy was performed in all patients. Only 1 (8.3%) patient had papillary thyroid lymph node metastasis in the follow-up period and modified radical lymph node dissection was performed. (Table 3) shows the details of breast surgeries performed in all cases. Immediate breast reconstruction type was silicone implantation and

Table 1. Characteristics of patients according to breast pathology

Patient no.	Age	Sex	Operation	BC histology	BC TNM#	ER/PR**	Neoadjuvant therapy	Adjuvant therapy
1	53	F	SM+ALND+TT	Invasive DC+DCIS	T2N1M0	60-70/5	None	AC+DT+Tamoxifen RT (66Gy)
2	50	F	MRM+IBR+TT	Invasive LC+DCIS	T2N2M0	60-70/60-70	None	AC+DT+TZM RT(50Gy)
3	49	F	SM+SLND+IBR+TT	Invasive DC+DCIS	T1cN0M0	Neg/Neg	None	Unknown regimen*
4	48	F	MRM+TT	Invasive BC	TXN2M0/T0N0M0	95/70	AC+DT+TZM	TZM RT (50Gy)
5	44	F	SM+SLND+TT	Invasive DC+DCIS	T1cN0M0	85/95	None	AC+Tamoxifen
6	63	F	MRM+TT	Invasive DC+DCIS	T2N1aM0	Neg/Neg	None	AC+TZM+ Tamoxifen
7	53	M	SiM+SLND+TT	Invasive DC+DCIS	T1cN0M0	90-95/30-40	None	Unknown regimen*
8	50	F	MRM+TT	Mixed carcinoma+DCIS	T2N3aM0	100/70	None	AC+DT RT(50Gy)
9	53	F	SM+SLND+TT	Invasive DC	T2N1M0	Neg/Neg	None	CEF+DT RT(50.4Gy)
10	70	F	MRM+TT	Invasive DC+DCIS	T2N2aM0	90-95/15-20	None	CEF+DT RT (50.4Gy)
11	62	F	SM+SLND+TT	Invasive DC+DCIS	T1cN0M0	90-95/10-15	None	RT (50.4Gy)
12	53	F	MRM+DBRi+TT	Invasive DC+DCIS	T2N3M0	Neg/Neg	None	CEF+DT+TZM RT(50Gy)

*: Adjuvant chemoradiotherapy given in another hospital.
**: Estrogen or progesteron receptor percentage.
#: Preoperative clinical and postoperative pathological TNM stage (Clinical TNM stage before neoadjuvant therapy and postoperative pathological TNM stage was both given for patient number 4)
AC: adriamycin+cyclophosphamide; ALND: axillary lymph node dissection; BC: breast cancer; CEF: Cyclophosphamide+Epirubicin+Flourouracil; DBRi: delayed breast reconstruction with implantation; DC: ductal carcinoma; DCIS: ductal carcinoma insitu; DT: docetaxel; ER: estrogen receptor; F: female; IBR: immediate breast reconstruction; LC: lobular carcinoma; M: male, MRM: modified radical mastectomy; PR: progesterone receptor; SM: simple mastectomy; SLND: sentinel lymph node dissection; SM: segmental mastectomy; RT: radiotherapy; TT: total thyroidectomy; TZM: trastuzumab

Table 2. Characteristics of patients according to thyroid cancer, survival and complications

Patient no.	Age	Sex	TC histology	TC size (mm)	RIA (mci)	Disease free survival (Months)	Follow-up (Months)	Postoperative Complication
1	53	F	PC	20	150	29	32	Re-exicision (Breast)
2	50	F	PC	15	None	22	22	SSI
3	49	F	PC	6	UR	12	12	None
4	48	F	PC	8	None	22	22	None
5	44	F	PC	17	100	14	14	None
6	63	F	PC	7	None	30	30	None
7	53	M	PC	6	UR	9	9	None
8	50	F	PC	2	None	12	12	Seroma
9	53	F	FC	20	100	8	8	None
10	70	F	PC	2	None	8	8	None
11	62	F	PC	1	None	4	4	None
12	53	F	PC	30	100	15	15	None

FC: follicular carcinoma; F: female, M: male; PC: papillary carcinoma; RIA: radioactive iodine ablation; SSI: surgical site infection; TC: thyroid cancer; UR: unknown regimen

Table 3. Breast surgery type which was performed for patients

Surgery type	Number of patients
MRM	4
SM+sLND	4
SM+aLND	1
SM+aLND+IBR	1
Simple mastectomy+sLND	1
MRM+IBR	1
MRM+DBR	1

aLND: axillary lymph node dissection; DBR: delayed breast reconstruction; IBR: immediate breast reconstruction; MRM: modified radical mastectomy; sLND: sentinel lymph node dissection; SM: segmental mastectomy

delayed breast reconstruction type was tissue expander and silicone implant.

Only 1 (8.3%) patient who underwent simple mastectomy (SM) with axillary lymph node dissection (LND) had positive surgical margins and reoperation with wide surgical resection was performed for this patient.

Histopathological findings

8 (66.8%) invasive ductal breast carcinoma + ductal carcinoma in situ and papillary thyroid carcinoma, 1 (8.3%) invasive lobular breast carcinoma + ductal carcinoma in situ and papillary thyroid carcinoma, 1 (8.3%) invasive breast carcinoma and papillary thyroid carcinoma, 1 (8.3%) mixed (invasive ductal and invasive mucinous) breast carcinoma + ductal carcinoma in situ and papillary thyroid carcinoma and 1 (8.3%) invasive ductal breast carcinoma and follicular thyroid carcinoma.

Treatment details

8 (66.8%) patients received adjuvant chemotherapy and radiotherapy, 1 (8.3%) patient received neoadjuvant and adjuvant chemotherapy and radiotherapy, 2 (16.6%) patients received adjuvant chemotherapy only and 1 (8.3%) patient received radiotherapy only. Only half of the patients (50%) received radioiodine ablation therapy.

Postoperative complications

Postoperative complications were due to mastectomy. The overall complication rate was 16.7%. These complications were seroma in 1 patient and wound infection in 1 patient, who were treated by conservative management. Average disease-free survival was 15.4 months (range between 4-30 months). Mean follow-up was 15.6 months (range between 4-32 months). No mortality was observed in the follow-up period.

Discussion and Conclusion

Breast cancer is the most common malignancy in women around the world. The 5-year relative survival rate of this cancer improved recently due to early detection and advances in treatment (11). As survival rates and incidence of this cancer has increased, the number of breast cancer survivors has also increased. During the diagnosis of breast cancer patients, detection of second primary malignancy is a significant issue.

Warren et al. (12) described synchronous primary cancers as a tumor diagnosed simultaneously with breast cancer or within a time interval of 6 months. The most common synchronous malignancy of breast cancer is thyroid cancer or vise versa (9, 13). There is an increased risk of secondary malignancy for breast or thyroid cancer survivors (14). Many studies have suggested that there is an association between thyroid diseases and breast carcinoma (15) whereas some authors did not find any obvious association (16).

The interactions between thyroid and breast disorders are based on hormonal and cellular receptor mechanisms (17, 18). In a recent prospective study, although no statistical difference was observed, thyroglobuline gene polymorphism and autoimmune thyroid disease was found to have high prevelance among breast cancer patients (19). Thyroid cancer survivors also have been found to develop breast cancer early, have more estrogen and progesterone receptor positive tumors, and have a greater incidence of mixed invasive cancer (20). Estrogen receptors have been found in thyroid tissue (21). Estrogen was found to have an influence on thyroid glands (22). The histology of the breast cancer that develops after thyroid cancer is different than the general population, with a greater percentage of mixed ductal and lobular invasive cancer and a greater percentage of ER/PR-positive tumors (20). In this current study, we found high percentage of ER/PR positive tumors (66.6%). Although indicated by many studies, an association between breast and thyroid cancer still remains controversial. All these studies suggest a possible interaction among breast and thyroid cancers.

The first malignancy diagnosed in our patients was breast cancer. Thyroid pathology was diagnosed either on physical examination or preoperative evaluation of breast cancer with FDG PET-CT scan. FDG PET-CT scan has been widely used for the diagnosis, initial staging, restaging, early treatment response assessment and evaluation of metastatic disease response of breast cancer (23). Although it has some disadvantages like irradiation, it is useful for detecting metastasis of breast cancer. It is reported to have a negative predictive value of 90 % for detection of thyroid nodules (24). It also detected 91.7 % of patients with thyroid pathology in our study.

Thyroid hormones have been found to stimulate cell proliferation in breast tissue, enhance the estradiol-mediated effects on cell proliferation, promote growth and induce the expression of progesterone receptors by mimicing the effects of estradiol (25, 26). Thyroid receptors found to be located in both normal and malignant breast cells (27). In a recent study, high free T4 levels and thyroid peroxidase antibody (TPO-Ab) levels were found to be associated with an increased risk of breast cancer (28). In a meta-analysis including 8 cross-sectional studies, authors found serum levels of free T3, TPO-Ab and thyroglobulin antibody to be significantly higher in patients with breast cancer than in healthy controls (29). Therefore, there is great evidence that the breast and thyroid tissue has some interactions on hormonal basis mainly influenced by the hormones secreted from thyroid gland. Thyroid receptors (TR) are encoded by two genes, TRα and TRβ, which are located on human chromosomes 17 and 3, respectively. In a recent study performed among Chinese people, aberrant expression and mutations of the TRβ1 gene were found to be associated with the development of breast cancer (30). Thus, thyroid hormone receptors play a role in breast cancer development.

Although the most common thyroid cancer type found to be associated with breast cancer is papillary thyroid cancer (85.9%), follicular cancer (11%) is also found to be increased in frequency (20). In our study, papillary thyroid cancer (91.7%) is also found to be the most common histologic type together with breast cancer whereas follicular cancer incidence was found as 8.3%.

In this current study we performed both mastectomy and thyroidectomy at the same time. Although our study has a limitation with short follow-up period, the main determinant of patients with synchronous breast and thyroid cancer is the breast cancer because of shorter survival rates. Performing mastectomy first and then thyroidectomy in the follow-up period may result in delay of the chemotherapy and radiotherapy. We believe that these two operations can be safely performed simultaneously as thyroidectomy adds only 60 minutes to the overall operation time, so it does not increase the risk for peroperative or postoperative complications due to anesthesia. Adjuvant radiotherapy for breast cancer reported to have some influence on thyroid tissue leading to hypothyroidism (31). Radiation is also known to increase risk for thyroid malignancy. Thus, it is better to diagnose thyroid pathology before breast cancer treatment and preoperative assesment of thyroid gland in patients diagnosed with breast cancer is crucial.

These different findings from literature represents one of the limitation of our study which was the result of small patient population. Retrospective design of this study is another limitation.

Although the exact mechanism of association between breast and thyroid cancers still remains unknown, synchronous presentation of these tumors can be seen. Thus, preoperative assesment of thyroid gland by physical examination is mandatory in patients diagnosed with breast cancer and if these patients are clinically negative for thyroid pathology radiological evaluation can be performed for them. Treatment for both of these cancers can be safely performed at the same time.

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