Clinical course and outcome of differentiated thyroid cancer patients with pregnancy after diagnosis of distant metastasis

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Abstract

Purpose

There is no sufficient data about the clinical course and outcome in thyroid cancer patients who become pregnant after diagnosis of distant metastasis (DM). The current study was conducted to collect information regarding the clinical and reproductive characteristics, and outcomes in thyroid cancer patients who became pregnant after being diagnosed with DM.

Methods

Records of 125 differentiated thyroid cancer (DTC) patients with age ≤ 45 years at DM diagnosis who had visited Ito Hospital from January 2005 to June 2021 were retrospectively reviewed. Among those 125 patients, 28 who became pregnant after DM diagnosis were classified as pregnant group, and the remained 97 patients were classified as comparator group.

Results

In pregnant group, the median age at malignancy diagnosis, DM diagnosis, and first pregnancy after DM diagnosis was 25 years (range, 4–41 years), 27 years (range, 11–41 years), and 32 years (range, 25–45 years), respectively. Fifty-five pregnancies and 40 live births were reported. Three patients had live births by embryo transfer. Other pregnancy outcomes were miscarriage ($n = 14$) and induced abortion ($n = 1$). No one died during the follow-up period in this study. The 10-year progression free survival (PFS) rates of pregnant and comparator group were 92.1% and 74.4%, respectively.

Conclusion

DTC patients who became pregnant after DM diagnosis had good survival. Our results add to the information required for counseling thyroid cancer patients who have concerns about their fertility in the future.

Introduction

Thyroid cancer is the most common type of endocrine-related malignancy [1]. Papillary thyroid carcinoma and follicular thyroid carcinoma are types of differentiated thyroid cancer (DTC) that account for $> 95\%$ of all thyroid carcinomas [2]. The prognosis of DTC is good, with a disease-specific survival rate $> 90\%$ [3]. However, some DTC patients experience recurrence, and the prognosis of patients with unresectable, advanced DTC remains poor [4]. Conditions involving distant metastasis (DM) of the lungs or bone are considered to be incurable, and radioactive iodine (RAI) or multi kinase inhibitor is treatment options in patients with these conditions [2, 5].

The staging system for thyroid cancer is unique, and age is considered an important prognostic factor. As per the American Joint Committee on Cancer (AJCC) Eighth Edition staging system of thyroid cancer, age of 55 years is used as a stratification value [6]. DTC patients with age < 55 years and DM are diagnosed Stage I, and the 10-year disease-specific survival (DSS) is over 90% [7]. Furthermore, some pediatric thyroid cancer patients have good prognosis even though they had DM at the time of diagnosis of malignancy [8]. Young thyroid cancer patients with DM survive longer than those with other malignancies, and some patients may wish to become pregnant.

Thyroid cancer is the second most common pregnancy associated with cancer [9]. Pregnancy-related hormones, such as estrogen and human chorionic gonadotropin, may favor the growth, progression, and spread of thyroid tumors [10, 11]. However, to our knowledge, there is no evidence showing that pregnancy worsens the prognosis of thyroid cancer [12, 13]. Xi et al. revealed that pregnancy does not affect the prognoses in DTC patients with lung metastasis [13].

In recent times, post-treatment life events, such as pregnancy and childbirth, have been considered an essential part of treatment planning for adolescent cancer patients because advances in cancer therapy have substantially increased the long-term survival rate of adolescent and young adult cancer survivors [14]. However, this issue remains unclear because there is insufficient data, especially in thyroid cancer patients with DM. Thus, we conducted an observational study to collect information regarding the clinical and reproductive characteristics, and outcomes in thyroid cancer patients who became pregnant after being diagnosed with DM. Furthermore, we compared the prognosis between those patients and comparator group.

Materials And Methods

Subjects

We screened records of 952 thyroid cancer patients with DM who had visited Ito Hospital from January 2005 to June 2021 were retrospectively reviewed. The inclusion criteria were female, age ≤ 45 years at DM diagnosis, differentiated thyroid cancer confirmed using surgical specimens. The exclusion criteria were male, age > 45 years at DM diagnosis, medullary thyroid cancer, poorly differentiated thyroid cancer, anaplastic thyroid cancer, previous history of other primary malignancy, and not meeting the criteria of DM. Since the success rate of fresh autologous treatment for women aged ≥ 45 years was very low (< 1%) and this age may be considered to be upper limitation of age for assisted reproductive technology (ART), we collected information of patients with age ≤ 45 years [15]. Finally, 125 patients were enrolled. Among those 125 patients, 28 who became pregnant after DM diagnosis were classified as pregnant group, and the remained 97 patients were classified as comparator group. Enrollment and participation flow diagram was shown in Fig. 1. Information regarding the patients' baseline and reproductive characteristics, laboratory data, RAI treatment history, disease progression, and death were subsequently collected for the analyses. Regular palpation examinations, and measurements of thyroid function and thyroglobulin (Tg) were performed every 3–6 months. A systemic survey such as computed tomography

(CT) or positron emission tomography (PET)/CT was performed every 12 months or when clinicians considered disease progression (e.g., elevation of serum thyroglobulin, appearance bone pain). During pregnancy, measurements of thyroid function and thyroglobulin were performed every 2–3 months to control thyroid stimulating hormone (TSH) levels in optimal range, and systemic survey was not performed. Fertility was assessed using the data collected using a self-administered questionnaire and medical records. The protocol employed in this retrospective study was approved by the Institutional Review Board of Ito Hospital (approval no. 336).

Definitions

DM was diagnosed based on CT, PET/CT, therapeutic ^{131}I -whole body-scan (^{131}I -WBS), and serum Tg levels [12]. Dosage of ^{131}I of 25 mCi or higher was considered as therapeutic doses. Overall survival (OS) was calculated as the duration from the point of diagnosis of malignancy to the date of death from any cause. Progression-free survival (PFS) was calculated as the duration from the point of diagnosis of DM to disease progression or the date of death from any cause. Disease progression was defined as $\geq 20\%$ increase in DM lesion volumes or the appearance of new lesions.

Statistical analysis

All the statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria) [16]. Categorical and continuous variables were compared using Fisher's exact test and Chi square test, and Mann–Whitney U test, respectively. PFS curves were constructed using the Kaplan–Meier method. Cox proportional hazards model was used to determine factors associated with PFS. A p value of < 0.05 was considered to indicate statistical significance.

Results

Baseline Characteristics

The baseline clinicopathological characteristics of the patients in pregnant and comparator group are shown in Table 1. In pregnant group, the median age at malignancy diagnosis and DM diagnosis was 25 years (range, 4–41 years) and 27 years (range, 11–41 years), respectively. Fifteen patients (54%) had DM at the time of malignancy diagnosis. Two patients had lung and bone metastases and the remaining 26 patients had only lung metastasis. The median Tg concentration measured at the time of DM diagnosis was 109.4 ng/dL (range, 0.5–7000 ng/dL). The median cumulative activity of ^{131}I was 200 mCi (range, 0–600). Among the 23 patients whose follow-up Tg data were available, 21 (91%) had lower Tg concentration at the point of first pregnancy after DM diagnosis than at the point of DM diagnosis; however, this difference was not statistically significant ($p = 0.151$). There were significant differences in age at diagnosis of malignancy, age at diagnosis of DM, and cumulative ^{131}I activity between two groups (Table 1).

Table 1
Baseline clinicopathological characteristics

	Pregnant group (n = 28)	Comparator group (n = 97)	p value
Age at malignancy diagnosis (years)	25 (4–41)	31 (6–45)	0.005
Age at distant metastasis diagnosis (years)	27 (11–41)	34 (6–45)	0.009
Histology, n (%)			0.532
Papillary	23 (82)	85 (88)	
Follicular	5 (18)	12 (12)	
Tumor-node-metastasis stage, n (%)			0.354
T			
T1-2	11 (39)	28 (29)	
T3-4	11 (39)	53 (55)	
TX	6 (22)	16 (16)	
N			0.551
N0	2 (7)	15 (15)	
N1	20 (71)	65 (67)	
NX	6 (22)	17 (18)	
M			0.070
M0	13 (46)	27 (28)	
M1	15 (54)	70 (72)	
Metastatic site, n (%)			0.792
Lung	28 (100)	90 (93)	
Bone	2 (7)	11 (11)	
Brain	0	1 (1)	
Thyroglobulin concentration at diagnosis of distant metastasis*	109.4 (0.5–7000.0)	80.0 (0.2–4800.0)	0.997
Anti-thyroglobulin antibody, n (%)			0.059

Numbers are presented as median (range). *Thyroglobulin concentrations at diagnosis of distant metastasis were unknown in five and 21 patients in pregnancy and comparator group, respectively.

	Pregnant group (n = 28)	Comparator group (n = 97)	p value
Positive	1 (4)	21 (22)	
Negative	19 (68)	51 (51)	
Unknown	8 (28)	25 (26)	
Cumulative ¹³¹ I activity (mCi)	200 (0-600)	130 (0-1059)	0.023
Multiple ¹³¹ I treatment, n (%)	18 (64)	57 (59)	0.820
Numbers are presented as median (range). ※Thyroglobulin concentrations at diagnosis of distant metastasis were unknown in five and 21 patients in pregnancy and comparator group, respectively.			

Reproductive characteristics

The reproductive characteristics are shown in Table 2. The median age at first pregnancy after DM diagnosis was 32 years (range, 25–45 years). Of the 28 patients, 10 (36%) had been pregnant at least once before they were diagnosed with DM. The median duration between the first pregnancy after DM diagnosis and the point of DM diagnosis was 4.8 years (range, 0.3–18.9 years), and the median duration between the first pregnancy after DM diagnosis and the last ¹³¹I treatment was 2.1 years (range, 0.5–14.5 years). The median TSH level measured at first pregnancy was 1.03 µIU/mL (range, 0.5–14.5 µIU/mL). Fifty-five pregnancies and 40 live births were reported. Three patients had live births by embryo transfer. Among 40 live births, the incidence of premature birth was 5.0% (n = 2), external abnormally was 5.0% (n = 2), small for dates was 2.5% (n = 1), and heavy for dates was 2.5% (n = 1), respectively. Other pregnancy outcomes were miscarriage (n = 14) and induced abortion (n = 1). Eight patients experienced miscarriage, and 3 of 8 reported multiple miscarriages.

Table 2
Reproductive characteristics

	n = 28
Age at first pregnancy after distant metastasis diagnosis (years)	32 (25–45)
Ever been pregnant before diagnosis of distant metastasis, n (%)	
Yes	10 (36)
No	18 (64)
TSH level at first pregnancy after distant metastasis diagnosis (μIU/mL)	1.03 (0.01–6.10)
Time to first pregnancy after distant metastasis diagnosis (years)	4.8 (0.3–18.9)
Time to first pregnancy after last radioactive iodine treatment (years)	2.1 (0.5–14.5)
Cumulative ¹³¹ I activity before first pregnancy (mCi)	200 (130–600)
Multiple ¹³¹ I treatment before pregnancy, n (%)	17 (61)
No. of pregnancies, n	55
Live birth, n	40
Women reporting miscarriage, n	14
Induced abortion, n	1
TSH, thyroid stimulating hormone.	
Numbers are presented as median (range). Among 40 live births, the incidence of premature birth was 5.0% (n = 2), external abnormally was 5.0% (n = 2), small for dates was 2.5% (n = 1), and heavy for dates was 2.5% (n = 1), respectively. Eight patients experienced miscarriage, and 3 of 8 reported multiple miscarriages.	

Survival and prognosis

The median follow-up time was 10.9 years (range, 4.2–32.5 years) in pregnant group and 6.6 years (range, 0.1–36.0 years) in comparator group. No one died during the follow-up period in this study. The results of the univariate and multivariate analyses of PFS in all 125 patients with DM are summarized in Table 3. An age of > 34 years (the median age of all 125 patients) ($p = 0.007$), multiple ¹³¹I treatment ($p = 0.039$), presence of distant metastasis other than lung ($p = 0.009$), and non-pregnancy ($p = 0.018$) were related to poor PFS in the univariate analysis. The 10-year PFS rates of pregnant and comparator group were 92.1% and 74.4%, respectively (Fig. 1). We performed multivariate analysis by including the factor of age, histology, multiple ¹³¹I treatment, distant metastatic site, and pregnancy. The multivariate analysis showed that multiple ¹³¹I treatment was independent prognostic factor for PFS ($p = 0.046$), and the history of pregnancy after DM diagnosis did not have negative effect on PFS. Among 28 patients in pregnant group, three patients exhibited disease progression during the follow-up period, and all the

events occurred after pregnancy. One patient developed bilateral lower extremity paralysis at 37 week of gestation because of bone metastasis progression. She underwent emergent and cesarean section, and lenvatinib was started after wound healing.

Table 3
Univariate and multivariate analysis of progression free survival

Variables	n = 125	Univariate analysis	Multivariate analysis		10-year PFS (%)
		p value	HR (95% CI)	p value	
Age (years)		0.007	2.302 (0.786–6.746)	0.128	
≤ 34	73 (58%)				90.2
> 34	52 (42%)				62.7
Histology		0.323	0.656 (0.150–2.870)	0.576	
Papillary	108 (86%)				84.2
Follicular	17 (14%)				60.8
Metastatic site		0.009	0.774 (0.162–3.703)	0.748	
Lung	112 (90%)				85.1
Other	13 (10%)				38.6
Multiple ¹³¹ I treatment		0.039	3.725 (1.026–13.530)	0.046	
Yes	75 (60%)				75.4
No	50 (40%)				90.3
Pregnancy		0.018	0.268 (0.061–1.181)	0.082	
Yes	28 (22%)				92.1
No	97 (78%)				74.4
CI, confidence interval; HR, hazard ratio PFS, progression free survival.					

Discussion

In this study, we investigated the clinical characteristics and outcomes in thyroid cancer patients who became pregnant after they were diagnosed with DM. All the 28 patients enrolled in the present study had very good prognosis; no one died in the follow-up period although the patients had DM. In addition, most patients whose 10-year PFS rate was 92.1% did not develop disease progression after pregnancy.

Age is a critical factor that influences the outcome in patients with well-DTC. The stratification age of 55 years is now used in the AJCC eighth edition staging system of thyroid cancer, and patients aged < 55 years are diagnosed to have Stage I or II disease. Nixon et al. reported that the 10-year DSS rates of Stage I and II patients were 99.5 % and 94.7%, respectively [7]. First, DTC patients with DM are generally treated with RAI. The response rate for lung metastasis showing iodine accumulation is estimated to be 17% for complete response, 44% for partial response, 33% for stable disease, and 6% for progressive disease in the Japanese revised clinical practice guidelines on the management of thyroid tumors [17]. The 10-year survival rate of patients with lung metastasis showing iodine accumulation was good, at 87%, and response to therapy was excellent, especially in young patients [18, 19]. This study included only female patients who became pregnant after being diagnosed with DM; all 28 patients were aged < 55 years at the time of DM diagnosis. Moreover, all the patients had lung metastasis. No one died during the follow-up period with a median duration of 15.5 years from the point of DM diagnosis, and the prognosis was considered very well, as in previous reports.

For DTC thyroid cancer patients, the effect of RAI on the reproductive function is an important consideration. Sawka et al. indicated that RAI treatment for DTC was generally not associated with a significantly increased risk of long-term infertility, miscarriage, induced abortions, stillbirths, or offspring neonatal mortality, or congenital defects [19]. Furthermore, Nies et al. reported that RAI treatment during childhood did not appear to impact the reproductive characteristics in female DTC patients [20]. In contrast, Ko et al. reported that patients treated with RAI had a lower successful delivery rate, particularly those aged 25–34 years as compared to those who did not undergo RAI [21]. In addition, Wu et al. revealed that the median time to the first live birth after DTC diagnosis was prolonged in women who received RAI than in those who did not [22]. Although it is controversial whether RAI affects the reproductive outcomes, RAI probably affects the timing of considering pregnancy in thyroid cancer patients. In Japanese patients with two or more unexplained consecutive miscarriages, the live birth rates ranged from 58.1–78.1% and were influenced by the maternal age [23]. As per other Japanese data, 33% of the women did not reach delivery (mean maternal age 33.1 years) [24]. The birth rate of the patients included in this study was 73% (40/55), similar to that reported for other Japanese populations. Therefore, the previous RAI treatment possibly did not affect the fertility in our subjects.

During pregnancy, iodine deficiency, the TSH receptor-stimulating effect of human chorionic gonadotropin, and high estrogen levels are believed to promote growth of benign and malignant nodules. Previous studies have shown no differences in the survival, recurrence, or death between pregnancy-associated thyroid cancer and cancer in age-matched non-pregnant women [10] However, a more recent study reported that persistence/recurrence of DTC is significantly higher in pregnant patients, suggesting that pregnancy could exert a negative prognostic role in DTC patients, and more careful follow-up is

needed in patients who are diagnosed with DTC during pregnancy or shortly thereafter [25]. Xi et al. reported that the 10-year PFS and OS rates were 63.22% and 85.77%, respectively, in the pregnancy group (n = 37) versus 58.13% and 81.95%, respectively, in the non-pregnancy group (n = 87); thus, pregnancy does not affect the DTC prognoses in patients with lung metastasis [13]. In this study, the 10-year PFS rate (92.1%) was better than that in a previous study. Young DTC patients may have good prognosis although they have DM. However, some DTC patients exhibited disease progression; therefore, we need to perform careful follow-up in patients with DM after pregnancy. Furthermore, one patient in this study started lenvatinib, a multi kinase inhibitor that is adapted for progressive and RAI-resistant DTC, after childbirth. In the future, for patients whose disease conditions were concerning, such as those considered for multi kinase inhibitor treatment, physicians need to be careful about recommending pregnancy.

Oncofertility care for female cancer survivors can include embryo/oocyte cryopreservation, ovarian tissue cryopreservation, and gonadotropin-releasing hormone agonist therapy. The Japan Agency for Medical Research and Development reports that > 1000 embryos or oocytes and > 100 ovarian tissue samples were cryopreserved for cancer patients between January 2011 and December 2015 [26]. Takahashi et al. analyzed the data of 67 Japanese women aged < 43 years who underwent oncofertility care. The study indicated that as spontaneous pregnancies were more common than ART pregnancies, pregnancy via not only ART, but also via the non-ART method is a viable option for young cancer survivors [14]. In our study, 40 live births were reported, and three patients had live births from pregnancies induce via embryo transfer. The timing of fertility preservation discussion may be different for each type of cancer, and the previous report included only one thyroid cancer patient. DTC patients have longer survival than those with other malignancies even in the presence of DM; thus, some patients may desire to become pregnant by using ART.

The present study has certain limitations. Firstly, this was a single-center retrospective investigation that included a relatively small number of patients. Secondly, there was a degree of selection bias in this study because patients with better physical condition and stable disease are more likely to decide to become pregnant after being diagnosed with DM. Finally, since systemic survey could not be performed during pregnancy, it was uncertain whether disease progression truly occurred after becoming pregnant. Despite these limitations, we believe that our results are important because to our knowledge, this is the first detailed report on the reproductive and clinical characteristics of DTC patients who became pregnant after being diagnosed with DM. Our study may help in making a decision regarding whether pregnancy is advisable for patients and physicians in the future.

In conclusion, the DTC patients who became pregnant after DM diagnosis had good survival. However, some patients exhibited disease progression of DM after pregnancy, and physicians need to perform careful follow-up in these patients. Furthermore, for patients whose disease conditions are concerning, the patients and physicians need to discuss the decision of becoming pregnant. We believe that our results add to the information required for counseling thyroid cancer patients who have concerns about their fertility in the future.

Declarations

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Conflicts of interest

The authors declare that they have no conflict of interest.

Availability of data and material

Not applicable.

Code availability

Not applicable.

Ethics approval

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Ito Hospital (approval number 336) and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consents

Informed consent was obtained from all individual participants included in the study.

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Figures

Figure 1.

Figure 1

Enrollment and participation flow diagram.

Figure 2.

Figure 2

Progression-free survival. The 10-year progression free survival rates of pregnancy and comparator were 92.1% and 74.4%, respectively (p = 0.018).