in vivo *30*: 713-716 (2016)

Synchronous and Metachronous Malignancies After Malignant Struma Ovarii in the SEER Database

ANDREA SISTI[1], JURI TASSINARI[1], GIUSEPPE NISI[1], LUCA GRIMALDI[1], GIOVANNI SISTI[2], MARIAROSARIA DI TOMMASO[2] and MASSIMILIANO FAMBRINI[3]

[1]Plastic Surgery Division, General and Specialist Surgery Department, University of Siena, Siena, Italy;
[2]Department of Health Sciences, Division of Obstetrics and Gynecology, University of Florence, AOU Careggi, Florence, Italy;
[3]Department of Biomedical, Clinical and Experimental Sciences, Division of Obstetrics and Gynecology, University of Florence, AOU Careggi, Florence, Italy

Abstract. *Background/Aim: Second primary tumors (SPTs) often occur, either synchronous or metachronous. Struma ovarii is a rare ovarian tumor represented by thyroid tissue in the ovary. Among other factors, production of thyroid hormones by the tumor or a shared genetic predisposition can further influence the development of SPTs. The occurrence of SPT, either synchronous or metachronous, following a long follow-up, has never been considered extensively. Patients and Methods: We analyzed the Surveillance, Epidemiology, and End Results (SEER) database from 1973 to 2011 to follow-up all the cases of malignant struma ovarii in an effort of calculate the occurrence of SPTs in this cohort of patients. Results: We identified 21 patients with malignant struma ovarii in the period between January 1973 and December 2011. In a follow-up period of 219.57 person-years, 3 patients had SPT. One patient had synchronous thyroid sclerosing carcinoma, 1 patient had metachronous papillary adenocarcinoma with a latent time of 7 years and 1 patient had synchronous salivary ductal carcinoma. Conclusion: Up to date, only thyroid synchronous tumors have been reported in the literature. A synchronous and a metachronous thyroid tumor, plus a synchronous salivary gland tumor, were found. A significant association between malignant struma ovarii and thyroid/salivary gland cancer is herein demonstrated.*

Second primary tumors (SPTs) often occur. The time lag between the first and second malignant transformation is variable. Two or more primary carcinomas can coexist at the time of diagnosis (synchronous) or develop consequently (metachronous), sometimes years after resection of the first primary.

Struma ovarii is a rare ovarian tumor comprising less than 2% of ovarian teratomas (1), with only 5% of these being malignant tumors (2). By definition, at least 50% of the tumor mass must be represented by thyroid tissue (3).

Diagnosis of struma ovarii is often incidental after histological examination of surgically resected ovarian mass as clinical presentation is usually asymptomatic, although it can occur with pelvic pain (4), abdominal swelling (5), hyperthyroidism (6), ascites (7) or pseudo-Meigs syndrome (8). Both Graves' disease that Hashimoto's thyroiditis have been diagnosed in some cases simultaneously with this cancer (9-11). Associated tumors have been sporadically described in the ovary (12), breast (13) and thyroid gland as follicular and papillary carcinoma (9, 14-16).

The occurrence of SPT, either synchronous or metachronous, following a long follow-up, has never been studied.

We analyzed the Surveillance, Epidemiology, and End Results (SEER) database (17) to follow-up all the cases of malignant struma ovarii in an effort to calculate the occurrence of SPT in this cohort of patients.

Patients and Methods

We used the incidence - SEER 9 Regs Research data (17). The SEER database is sponsored by the National Cancer Institute and has reported cancer incidence and survival since its institution in 1973.

It is a population-based registry that covers approximately 26% of the United States population and captures 98% of all cancer cases in its surveyed geographic area. The SEER registry was examined from 1973 to 2011 and cases of malignant struma ovarii were identified.

Correspondence to: Andrea Sisti, MD, Plastic Surgery Division, General and Specialist Surgery Department, University of Siena, Siena, Italy. Tel: +39 0577-585158, e-mail: asisti6@gmail.com

Key Words: Malignant struma ovarii, salivary gland cancer, SEER, second primary tumors, thyroid gland cancer, salivary gland cancer.

The database contains information on patient demographics, primary cancer site, histology, methods of diagnostic confirmation, treatment regimens (including surgery and radiation therapy) and year of death. Institutional Review Board approval was not required for this study as the SEER database is free of any sensitive patient information or identifiers.

The SEER 9 registries are Atlanta, Connecticut, Detroit, Hawaii, Iowa, New Mexico, San Francisco-Oakland, Seattle-Puget Sound and Utah. Data are available for cases diagnosed from 1973 and later for these registries with the exception of Seattle-Puget Sound and Atlanta. The Seattle-Puget Sound and Atlanta registries joined the SEER program in 1974 and 1975, respectively.

We used the SEER*Stat software (18) to estimate the incidence of SPT in the struma ovarii cases.

For the identification of SPTs, SEER takes account of histology, site, laterality and time since initial diagnosis to identify multiple primary cancers (19, 20).

In the distinction between synchronous and metachronous SPT, we used the widely-accepted criteria established by Warren and Gates (21) as follows: synchronous tumors were defined as second primary tumors that were diagnosed within 6 months of the first primary tumor; metachronous cancers were defined as those that were detected after an interval of more than 6 months.

The SEER*Stat software (18) gives also the ratio between observed/expected (O/E) cases, calculating significance levels with the Fisher's exact test.

A p-value less that 0.05 was considered statistically significant.

Results

We identified 21 patients with malignant struma ovarii in the period between January 1973 and December 2011. In a follow-up period of 219.57 person-years, 3 patients had SPT (Table I).

One patient had synchronous thyroid sclerosing carcinoma, 1 patient had metachronous papillary adenocarcinoma with a latent time of 7 years and 1 patient had synchronous salivary ductal carcinoma.

All patients had surgery of the primary site without subsequent radiotherapy.

The O/E ratio to the general population was 41.88 for thyroid cancers and 344.10 for salivary gland tumors, both of them resulted to be statistically significant (Table II).

The risk of all solid tumors, in general, was not augmented when compared to the general population (Table II).

Discussion

We found a significant association between malignant struma ovarii and thyroid/salivary gland cancer.

Up until now, only thyroid synchronous tumors have been reported in the literature (9, 14-16). We found a synchronous and a metachronous thyroid tumor, plus a synchronous salivary gland tumor.

The current, generally accepted, main theories have proposed the co-occurrence of struma ovarii and thyroid cancer as a mutagenic trigger causing independent genetic events (14).

The risk of further primary cancers might be due to persisting effects of genetic and behavioural risk factors, long term side-effects of chemo- and radiotherapy, as well as increased diagnostic sensitivity.

We suppose that a common genetic mutagen can affect different body sites to develop similar tumoral mutations. One can also speculate that the thyroid hormonal production by the ovarian tumor can further influence the development of other tumors in the subsequent years. Treatment for struma ovarii involves surgical resection due to the risk of malignant degeneration or hyperthyroidism.

Due to the rarity of thyroid cancer arising within struma ovarii, optimal management has not yet been defined (16). Surgical management of the primary tumor and the thyroid gland, as well as the potential indications for adjuvant treatment, have not been standardized.

Pelvic management includes unilateral cystectomy as main procedure. Eventually, the surgeon can decide to perform unilateral salpingo-oophorectomy or total abdominal hysterectomy with bilateral salpingo-oophorectomy, depending on the grade of the tumor and the patient's fertility wellness. When extra-ovarian extension or distant metastases are present, total thyroidectomy may be performed to facilitate radioactive iodine (RAI) therapy.

The role of thyroidectomy and RAI in localized, non-metastatic struma ovarii thyroid cancer is not well-defined, since the natural history of the disease is not yet well-known (22). The few studies available about follow-up of struma ovarii have showed an overall good prognosis and a low percentage of recurrence of well-differentiated thyroid cancer arising in struma ovarii (16, 23), even if very aggressive forms have been described (24).

Our finding of two second primary thyroid tumors coincidentally or after struma ovarii, reinforces the side of an aggressive management comprehending a thyroidectomy (25). The association with a salivary gland tumor is new and further studies are needed to assess the relationship between these two tumors. There seems to be little evidence of the direct relationship between the function of the thyroid gland and the salivary glands from experiments in rats and mice (26, 27). Thyroid diagnostic imaging at the time of the diagnosis of struma ovarii is very important in order to find any other synchronous tumor present in other locations or any metastases. This can be performed by ^{124}I-positron emission tomography/computed tomography (PET/CT). Magnetic resonance (MR) imaging and ultrasound (US) are useful to unearth pathological structures located in soft tissues (28-30). In addition, a check-up for synchronous salivary gland tumor could be of certain importance.

In our opinion, the extension of surveillance for a longer follow-up period should be carefully evaluated in every patient affected by struma ovarii, in search of subsequent development of thyroid cancers or other tumors after struma ovarii.

Table I. *Second primary tumor (SPT) after struma ovarii identified.*

SPT	Year/Age at diagnosis of struma ovarii	Year/Age at diagnosis of SPT	Person-time calculated of the event	Person-years at risk
Thyroid (papillary adenocarcinoma)	1984/45	1991/50	7.25	219.57
Thyroid (non-encapsulated sclerosing carcinoma)	2003/54	2003/55	0.08	219.57
Salivary gland (infiltrating duct carcinoma)	2010/52	2010/52	0.42	219.57

Table II. *Incidence analysis of second primary tumor (SPT) in various body sites in comparison to the expected incidence in the general population.*

	Observed	Expected	O/E	CI 95% (lower-upper)	Excess risk	Persons	Person-years at risk	Mean person-years at risk
All sites	3	1.24	2.42	0.5-7.07	80.19	21	219.57	10.46
All sites excluding non-melanoma skin	3	1.24	2.43	0.5-7.09	80.35	21	219.57	10.46
All solid tumors	3	1.13	2.65	0.55-7.74	85.02	21	219.57	10.46
Salivary gland	1	0	344.10	8.71-1,917.19	45.41	21	219.57	10.46
Thyroid	2	0.05	41.88	5.07-151.3	88.91	21	219.57	10.46

O/E, Observed/expected; CI, confidence interval.

Funding

None.

Conflicts of Interest

None.

References

1 Rosenblum NG, LiVolsi VA, Edmonds PR and Mikuta JJ: Malignant struma ovarii. Gynecol Oncol *32*: 224-227, 1989.
2 Talerman A: Germ cell tumors of the ovary. Curr Opin Obstet Gynecol *9*: 44-47, 1997.
3 Dardik RB, Dardik M, Westra W and Montz FJ: Malignant struma ovarii: two case reports and a review of the literature. Gynecol Oncol *73*: 447-451, 1999.
4 Halpenny DF, O'Brien J, Ibrahim MM, Crotty R and Torreggiani WC: An unusual cause of pelvic pain: struma ovarii. JBR-BTR *92*: 239-241, 2009.
5 Barrera JR, Manalo LA and Ang FL: Papillary thyroid-type carcinoma arising from struma ovarii. BMJ Case Rep: Jul 11, 2012. doi:10.1136/bcr.03.2012.6145.
6 Chiofalo MG, Misso C, Insabato L, Lastoria S and Pezzullo L: Hyperthyroidism due to coexistence of Graves' disease and Struma ovarii. Endocr Pract *13*: 274-276, 2007.
7 Sinha NK: Struma ovarii with elevated ca-125 levels and ascites mimicking advanced ca ovary. J Clin Diagn Res *8*: 140-141, 2014.
8 Sivrioglu AK, Saglam M, Sonmez G and Deveer M: Pseudo-Meigs' syndrome associated with struma ovarii. BMJ Case Rep 2013, 2013. doi:10.1136/bcr-2013-009189.
9 Anastasilakis AD, Ruggeri RM, Polyzos SA, Makras P, Molyva D, Campenni A, Gkiomisi A, Balaris C, Fotiadis PP, Tuccari G and Papachatzopoulos S: Coexistence of Graves' disease, papillary thyroid carcinoma and unilateral benign struma ovarii: case report and review of the literature. Metabolism *62*: 1350-1356, 2013.
10 Wong LY and Diamond TH: Severe ophthalmopathy developing after treatment of coexisting malignant struma ovarii and Graves' disease. Thyroid *19*: 1125-1127, 2009.
11 Morrissey K, Winkel C, Hild S, Premkumar A and Stratton P: Struma ovarii coincident with Hashimoto's thyroiditis: an unusual cause of hyperthyroidism. Fertil Steril *88*: 497 e415-497, 2007.
12 Dhingra KK, Jain P, Garg A and Khurana N: Coexistent struma ovarii and serous cystadenofibroma in the same ovary. Int J Gynecol Pathol *28*: 231-233, 2009.
13 Frattini F, Rovera F, Rausei S, Dionigi G, Boni L, Biondi A and Dionigi R: Struma ovarii in breast cancer. Updates Surg *63*: 143-144, 2011.
14 Leong A, Roche PJ, Paliouras M, Rochon L, Trifiro M and Tamilia M: Coexistence of malignant struma ovarii and cervical papillary thyroid carcinoma. J Clin Endocrinol Metab *98*: 4599-4605, 2013.
15 Krishnamurthy A, Ramshankar V, Vaidyalingam V and Majhi U: Synchronous papillary carcinoma thyroid with malignant struma ovarii: A management dilemma. Indian J Nucl Med *28*: 243-245, 2013.
16 Marti JL, Clark VE, Harper H, Chhieng DC, Sosa JA and Roman SA: Optimal surgical management of well-differentiated thyroid cancer arising in struma ovarii: a series of 4 patients and a review of 53 reported cases. Thyroid *22*: 400-406, 2012.
17 Surveillance, Epidemiology, and End Results (SEER) Program SEER*Stat Database: Incidence - SEER 9 Regs Research Data,

Nov 2013 Sub (1973-2011) <Katrina/Rita Population Adjustment> - Linked To County Attributes - Total U.S., 1969-2012 Counties, National Cancer Institute, DCCPS, Surveillance Research Program, Surveillance Systems Branch, released April 2014, based on the November 2013 submission at www.seer.cancer.gov.

18 Surveillance Research Program SEER*Stat software version 8.1.5. at seer.cancer.gov/seerstat.

19 Hwang LJ, Altekruse S, Adamo M and Sun L: SEER and NAACCR data completeness methods: how do they impact data quality in Central Cancer Registries? J Registry Manag *39*: 185-186, 2012.

20 Johnson CH, Phillips JL, Stewart AK, Lewis M, Phillips JL, Adamo P, Ries L and Stinchcomb D: Clarification from the CoC, NPCR, SEER technical workgroup. J Registry Manag *38*: 166-168, 2011.

21 Warren S: Multiple primary malignant tumors: A survey of the literature and a statistical study. Am J Cancer: 1358-1414, 1932.

22 Roth LM and Talerman A: The enigma of struma ovarii. Pathology *39*: 139-146, 2007.

23 Hemli JM, Barakate MS, Appleberg M and Delbridge LW: Papillary carcinoma of the thyroid arising in struma ovari – report of a case and review of management guidelines. Gynecol Endocrinol *15*: 243-247, 2001.

24 Marcy PY, Thariat J, Benisvy D and Azuar P: Lethal, malignant, metastatic struma ovarii. Thyroid *20*: 1037-1040, 2010.

25 Shrimali RK, Shaikh G and Reed NS: Malignant struma ovarii: the west of Scotland experience and review of literature with focus on postoperative management. J Med Imaging Radiat Oncol *56*: 478-482, 2012.

26 Feng YS and Wase AW: Some salivary-thyroid gland relationships. Acta Endocrinol (Copenh) *23*: 413-418, 1956.

27 Kawada J: On the functional correlation between salivary glands and other endocrine organs. V. Changes in rat salivary glands following thyroidectomy, administration of antithyroid drugs and thyroxine-treatment. (Studies on the physiological chemistry of the salivary glands. 63.). Endocrinol Jpn *8*: 259-271, 1961.

28 Dujardin MI, Sekhri P and Turnbull LW: Struma ovarii: role of imaging? Insights Imaging *5*: 41-51, 2014.

29 Freesmeyer M, Schleussner E and Winkens T: Diagnosis of Struma Ovarii in a Patient with Papillary Thyroid Carcinoma - Verification *via* ^{124}I-PET/US Fusion. Ultraschall Med *35*: 368-370, 2014.

30 Lopci E, Colombo P, Rodari M, Lania A, Vitobello D, Leonardi L and Chiti A: Imaging struma ovarii by means of 124I-Na PET/CT. Nucl Med Rev Cent East Eur *16*: 95-96, 2013.

Received April 5, 2016
Revised May 5, 2016
Accepted June 5, 2016