ABSTRACT

Objectives

Radioactive iodine (RAI) is widely used as a treatment for differentiated thyroid cancer following total thyroidectomy. There is a risk of second primary malignancy (SPM) in these patients which is estimated between 0-5% although research to support this is limited. The primary aim of this study was to ascertain the rate of SPM in patients who have undergone RAIT for thyroid cancer. The secondary objectives were to assess whether the risk is dose dependant and examine the overall survival and recurrence rates.

Design

A retrospective review of all patients treated with radioactive iodine for thyroid cancer between 2002 and 2014. Patient information was collected from a structured database. Data regarding second cancers and recurrence rates was obtained from an online clinical portal. Follow up was 5 years minimum.

Results

199 patients underwent RAI treatment. Median age was 53. 71.4% patients were female and 28.6% were male. All patients underwent total thyroidectomy. 13.6% underwent total thyroid and central neck dissection. 11% underwent total thyroidectomy and lateral neck dissection. 5.5% required post-operative radiotherapy. 12% patients developed recurrent thyroid cancer. 8% developed a SPM of which prostate, skin, head and neck SCC were the most common. A dose ≥3.7 Gigabecquerel (GBq) was statistically significantly more likely to lead to a SPM with a P value of 0.041 (95% CI -0.52 – 0.01318).

Conclusions

Increased risk of developing a second primary malignancy should be taken into account, especially in younger patients with low risk disease, when deciding on RAIT.

Key words

Radioactive iodine, Differentiated thyroid cancer, Second primary malignancy, Radioiodine, Thyroid cancer

Level of Evidence: Level 4

Key Points

1. RAIT is regularly used following resection of primary thyroid cancer to reduce recurrence rate by eradicating any residual foci of cancer and also by facilitating post-treatment surveillance with thyroglobulin measurements.
2. Long-term side effects of RAIT include infertility, pulmonary fibrosis, and risk of second primary malignancies (SPM) with the estimated risk between 0-5% of patients treated.
3. This study of 199 patients identified a SPM rate of 8% of which prostate, skin, head and neck SCC were the most common.
4. A dose ≥3.7 Gigabecquerel (GBq) was statistically significantly more likely to lead to a SPM ($P = 0.041$).
5. SPM risk should be taken into account particularly when considering use of RAIT in younger patients with low risk disease.

INTRODUCTION

Differentiated thyroid cancer (DTC) is the most common malignant endocrine tumour. There has been a dramatic rise in the incidence over the last 3 decades. This is thought, in part, to be due to increased detection of incidental microcarcinomas (1,2)
The initial treatment of DTC is to resection of the primary tumour with total thyroidectomy although for microcarcinomas a hemithyroidetomy may be curative. (3,4,5)
Following surgical resection risk stratification is performed and adjunctive treatments, such as radioactive iodine treatment (RAIT) and thyroid stimulating hormone (TSH) suppression are employed which will help to reduce the risk of recurrence (1,6).

The role of RAI is primarily to reduce recurrence rates by eradicating any residual foci of cancer and secondly to ablate any remaining normal thyroid tissue facilitating post treatment surveillance with thyroglobulin measurements (7). The commonest acute complications of RAI are sialadenitis, nausea, dysgeusia and neck discomfort. Long-term side effects include infertility, pulmonary fibrosis, and risk of second primary malignancies (SPM) with the estimated risk between 0-5% of patients treated (8-13).

It is now suspected that rate of SPM may be higher but there is still a lack of evidence to support this. Due to the good prognosis of DTC and quite often the young age that it is diagnosed at establishing the risk of SPM is important particularly when considering its use in low risk cancers (7).

The primary aim of this study was to ascertain the rate of SPM in patients who have undergone RAIT for thyroid cancer. The secondary objectives were to assess whether the risk is dose dependant and examine the overall survival and recurrence rates.

DESIGN

SETTING

We conducted a retrospective study of 199 patients treated with thyroid surgery and RAI for thyroid cancer between January 2002 and December 2014. Minimum follow up was 5 years. Surgery was carried out in one of three centres however all radioactive iodine treatment was then centralised to one centre. The STROBE checklist for cohort studies was followed.

DATA SOURCES

Details of all patients who had undergone RAIT were retrieved from the local Oncology radioiodine registry. Patient demographics including age, gender and previous malignancies, along with treatment methods and details of second primary malignancies, were obtained from the online clinical portal systems at the three centres where the patients underwent surgery.

STATISTICAL METHODS

We used descriptive methods for establishing the incidence of second malignancies and recurrence rates. SPSS version 22 was used to determine the statistical significance, odds ratio and relative risk of whether developing a second primary was dose dependant. Statistical significance was defined as a P value of ≤ 0.05.

RESULTS

199 patients underwent RAIT over this time period. Median age was 53. 142 patients (71.4%) were female and 57 (28.6%) were male. Table 1 details the histology results from this patient group.

All patients underwent total thyroidectomy but depending on the presence of metastatic disease some patients also required central or lateral neck dissections and external beam radiotherapy as shown in Table 2.

The mean dose of RAI given was 3.4GBq with a range of 0.8 – 7.1GBq. The overall survival rate amongst this cohort was 88.0% (175/199) with a recurrence rate of 12.0% (24/199) with a mean time to recurrence of 4.67 years (range 1-13 years)

The rate of SPM was 8.0% (16/199 patients) and the mean latency period for the second malignancy was 5 years (range 1-16 years). Table 3 demonstrates the type of SPM found in each patient during the follow up and the doses of RAI that these patients received.

Student t test was performed to assess whether the dose of RAI was related to the risk of suffering with SPM. It was determined that a dose ≥3.7Gbq was statistically significantly more likely to lead to a SPM with a P value of 0.041 (95% CI -0.52 – 0.01318).

DISCUSSION

There are around 3,700 new cases of thyroid cancer in the UK every year accounting for 1% of all new cancer cases. Incidence rates have increased by over 2/3 in the UK over the last 10 years and they are predicted to rise by 74% by 2035. Despite the increasing incidence of thyroid cancer, the mortality rates in the UK have decreased by almost half (47%) since the early 1970s, with approximately 400 deaths a year. (14,15).

A significant number of these patients will undergo RAIT. Current guidelines from the British Thyroid Association recommend that RAIT be given to all patients with distant metastases, extrathyroidal extension of the tumour or a tumour >4cm in size. BTA does not recommend RAI for patients with a unifocal cancer of <1cm, or multifocal cancer when all foci are <1cm providing there are no high-risk features. For patients who do not fall into either of these categories risk stratification is carried out taking into account age, histology and lymph node involvement. Based on this information the decision of whether to give RAI is made on an individual basis (1). It is important to consider need for RAIT in this later group of patients', particularly young patients with low risk disease, due to the recognised risk of SPM.

Several studies have addressed the risk of SPM following RAIT. Haematological malignancies such as leukaemia are the most commonly documented followed by solid malignancies such as salivary gland and kidney. These findings can be explained as a result of the accumulation of RAI in the salivary glands and bone marrow and subsequent excretion through the kidneys. Increased rates of prostate, adrenal, breast, central nervous system and colorectal cancers have also been reported although the reasons behind this are less clear (9,16,17).

Seo et al (2015) looked specifically at the association of RAI dose with development of leukaemia in a population of 211,360 patients. RAI dosage was divided into low dose (≤1.1 GBq), moderate dose (1.1-3.7 GBq), high dose (3.7-5.6 GBq) and very high dose (>5.6 GBq). They established that doses > 3.7 GBq increased significantly as early as 9 months following RAI therapy (18).

Silva- Vierira et al (2017) examined the rate of SPM in 2031 patients diagnosed with DTC, 77% of whom underwent RAIT. The rate of SPM was 8.2% in the RAI therapy group compared to 4.5% in those who didn't have RAIT. They established that use of doses >200

Millicurie (mCi) (7.4 GBq) led to a statistically significantly greater risk of SPM concluding that given the excellent survival rates, particularly in low risk patients, we should be carefully considering the use of RAIT (20). Teng et al also observed a statistically significantly increased risk of SPM in cumulative doses of RAI >150mCi (5.5 GBq) in a population group of 20 235 patients (P=<0.001) (20).

Our study found the rate of SPM to be 8% with haematological, prostate, skin and head and neck cancers being the most common. We identified that a RAI dose of ≥100 mCi (3.7 GBq) was associated with a statistically significantly greater risk of developing a SPM which is comparable to similar studies. As eluded to in similar studies it isn't possible to attribute all of the SPM that we identified to RAIT. This increased risk may simply be a consequence of regular and thorough surveillance of these patients (17).

This study was limited by the small numbers treated and lack of inclusion of lifestyle factors such as family history of malignancy, smoking and alcohol history which may impact on their risk of developing a SPM. One patient within the study was found to have anaplastic thyroid cancer. The histology initially demonstrated follicular thyroid carcinoma at which point the patient was treated with RAI. The histology was re-examined due to the rapidly progressive nature of the disease and diagnosis was corrected to anaplastic cancer.

CONCLUSION

In conclusion, we found that patients undergoing RAIT for thyroid cancer are at an increased risk of developing SPM and the findings of our study reinforce this. We have established that this should be taken into account particularly when considering use of RAIT in younger patients with low risk disease. We do, however, require further research specifically looking at SPM risk in RAI treated patients compared to the general population as well as the consequence of RAI dose on risk of developing SPM.

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TABLE 1

THYROID CANCER TYPE	**NUMBER OF PATIENTS**
Papillary	116 (58.3%)
Follicular	42 (21.1%)
FVPTC	18 (9.0%)
Hurtle Cell	9 (4.5%)
Medullary	1 (0.5%)
Anaplastic	1 (0.5%)
Not Documented	12 (6.0%)

Table 1: Tumour Characteristics

TABLE 2

SURGICAL INTERVENTION	**NUMBER OF PATIENTS**
TOTAL THYROIDECTOMY ONLY	139 (69.8%)
TOTAL THYROIDECTOMY & CENTRAL NECK DISSECTION	27 (13.6%)
TOTAL THYROIDECTOMY & CENTRAL & LATERAL NECK DISSECTION	22 (11.0%)
EXTERNAL BEAM RADIOTHERAPY	11(5.5%)

Table 2: Treatment of Differentiated Thyroid Cancer (DTC)

TABLE 3

TYPE OF CANCER	**PATIENTS NUMBER**	**PATIENT AGE**	**DOSE OF RAI GIGABECQUERELS (GBq)**
HEAD & NECK SCC	2	Patient 1: 49 Patient 2: 64	Patient 1: 3.7 Patient 2: 7.1
PROSTATE	3	Patient 1: 69 Patient 2: 56 Patient 3: 75	Patient 1: 3.7 Patient 2: 3.6 Patient 3: 3.8
OVARIAN	1	51	1.1
SKIN CANCER	2	Patient 1: 43 Patient 2: 60	Patient 1: 3.7 Patient 2: 3.6
BREAST	1	57	3.7
HAEMATOLOGICAL	2	Patient 1: 70 Patient 2: 71	Patient 1: 3.7 Patient 2: 3.7
SALIVARY GLAND	1	28	3.6
CERVIX	1	23	3.7
BRAIN	1	70	3.9
COLORECTAL	1	50	1.1
SPINAL CORD	1	53	4.1

Table 3: Second Primary Malignancies (SPM)