Original Article

Clinical predictors of I-131 therapy failure in differentiated thyroid cancer by machine learning: A single-center experience

ABSTRACT

Well-differentiated thyroid carcinoma is predominantly a slow-growing malignancy, amendable to treatment, and has an excellent prognosis following thyroidectomy and radioiodine (RAI) therapy. However, patients who fail the initial RAI treatment attempt may require repeated RAI or other treatments and with this, comes an associated impact on patient quality of life. Therefore, the anticipation of patients in whom there is a higher risk of RAI failure may help in patient risk stratification and subsequent management. We conducted a retrospective review to determine the factors associated with initial RAI therapy failure in well-differentiated thyroid cancer patients. Using scikit-learn from Python, we implemented a machine-learning algorithm to determine the clinical patient factors associated with a higher likelihood of treatment resistance. We found that clinical factors such as tumor focality ($P = 0.026$) and lymph node invasion at surgical resection ($P = 0.0135$) were significantly associated with initial treatment failure following RAI. Elevated serum thyroglobulin (Tg) and Tg antibody levels following surgery but before RAI were also associated with treatment resistance ($P < 0.0001$ and $P = 0.011$ respectively). Less expected factors such as decreased time from surgery to RAI were also associated with treatment failure, however not to a statistically significant degree ($P > 0.064$). Clinical outcomes following RAI can be stratified by identifying factors that are associated with initial treatment failure. These findings can help restratify patients for RAI treatment and change patient management in certain cases. Such stratification will ultimately help to optimize successful treatment outcomes and improve patient quality of life.

Keywords: Machine learning, radioiodine ablation, restratification, thyroglobulin, thyroid cancer

INTRODUCTION

Thyroid cancer is one of the most common endocrine malignancies, and differentiated thyroid cancer (DTC) comprises more than 90% of all thyroid carcinomas.[1] Greater than 85% of DTC cases are due to papillary thyroid cancer (PTC), making them by far the most common type.[1] Standard treatment of DTC generally includes thyroidectomy followed by radioiodine (RAI) ablation of remnants[2,3] with iodine-131 (I-131) and subsequent initiation of thyroid hormone replacement therapy. This general treatment approach usually results in successful disease remission and most patients have an excellent prognosis. Treatment success is measured by undetectable or significantly low serum thyroid tumor marker thyroglobulin (Tg) and anti-Tg antibodies. In addition, disease remission usually includes

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an absence of iodine-concentrating tissue seen on follow-up imaging.[1] Initial radioiodine dosing is selected based on the intent of therapy and generally, this is for complete ablation of any remnant thyroid tissue.[2]

Yet, despite the generally high success rate in DTC treatment following thyroidectomy and initial RAI, treatment failure can arise. A novel restratification of patients in the management of PTC has been proposed based on the response to initial therapy and this has been reported to have a better correlation with long-term outcomes.[3] The American Thyroid Association (ATA) initial Risk Stratification System was recommended in 2009 based on its utility in predicting the risk of disease recurrence. Nevertheless, some studies have found poor agreement between initial risk stratification and the actual outcome after evaluation in response to treatment.[2,3] There is a relative paucity of published data which correlates risk factors predicting failure of initial therapy and the likelihood of disease recurrence.[4] Given the high prevalence of DTC[5] and the possibility of risk for negative outcomes even after recommended treatment, a study to evaluate the clinical factors predictive of failure of initial radioiodine therapy in thyroid cancer patients is warranted. We report here our experience with RAI therapy for DTC in patients treated over an approximately 10-year period. We performed a retrospective review of patients with DTC who underwent surgical resection and initial dosing with I-131 for radioiodine ablation in our clinic. Patients who had persistent disease either indicated by biochemical serum markers or by evidence of disease on follow-up imaging after the initial dose of radioiodine were considered to have failed initial treatment. By pooling the electronic medical-record data, we looked at patient clinical features and examined their relationship to initial RAI treatment failure.

MATERIALS AND METHODS

This is a retrospective single-center study conducted at our institution which was sent to the Institutional Review Board (IRB submission 1556801-1), reviewed and found exempt from IRB review (exemption category #4 [ii]) and subsequently approved under de-identification. We performed a search in our electronic medical record system (Epic) for all patients with a diagnosis of DTC established by histopathology who underwent near-total or total thyroidectomy and subsequent I-131 therapy for the first time from November 2009 to January 2020 in the Nuclear Medicine Department at our institution. We excluded those patients who did not have follow-up diagnostic imaging (radioiodine whole-body scan, positron emission tomography-computed tomography [PET/CT]) and/or Tg and anti-Tg antibody serum markers as we would not be able to determine their response to initial therapy. As per our institutional protocol, patients scheduled for RAI were placed on a low-iodine diet 2 weeks before the treatment date. Subsequently, on the 2 days preceding treatment, intramuscular injections of 0.9 mg recombinant thyroid stimulating hormone (TSH) (thyrogen) each were administered. In these cases, the serum TSH level was not measured explicitly as it was assumed to be adequately elevated for treatment. On rare occasions, the referring physician would request that the patient only have their replacement thyroid hormone withheld 4–6 weeks before treatment and then a serum TSH level was measured to be sure it was above at least 30 u (IU)/mL before RAI dosing and treatment. Both Tg and anti-Tg antibodies were measured at the time of RAI or at follow-up and most often this was done following stimulation with recombinant TSH.

After review of the medical records, we identified 107 adult patients who met the inclusion criteria. Patients ranged in age from 18 to 79 years old and $n = 73$ female, $n = 34$ male [Table 1]. Sixteen patient variables were included in our study: age at the time of diagnosis, gender, previous thyroid disease, type of thyroidectomy, extent of disease and lymph node involvement at surgery, histopathological variant, size of primary tumor, multifocality, I-131 dose administered, time from surgery to RAI therapy, pre-RAI and post-RAI Tg and anti-Tg antibody serum levels respectively, and time from RAI to follow-up. The outcome was clinical response to RAI therapy. Treatment failure is defined as persistent abnormally elevated Tg values (biochemical incomplete response to therapy), and persistent loco-regional or distant metastasis identified by follow-up imaging such as on a radioiodine scan or 18F-fluorodeoxyglucose (FDG) PET/CT scans (anatomic incomplete response). Of the 107 patients included in our study, 46 had treatment failure following initial RAI. Incomplete response to therapy, the nomenclature used in the new ATA guidelines, is used interchangeably with treatment failure.

We utilized a multivariable logistical regression (machine learning) analysis program in Python (v 2.7). Using the popular set of machine learning libraries in Python with Sklearn (scikit-learn, Python) we looked at features from our tabulated clinical dataset (Excel, Microsoft Office 2019) which were significantly associated with resistance to RAI treatment.[6-8] We used a random forest classifier and then performed a test for significance to obtain *P* values from the various contribution each variable had on whether or not the patient failed therapy [Table 2]. Our model was cross-validated and checked by data-shuffling. For the

Table 1: Patient demographics

Clinical parameter	*n* Variable range, number of values (*n*)	Mean±SD
Male/female	Male *n*=34, female *n*=73	
Treatment failure following initial RAI	*n*=46 (from serum biomarkers *n*=35, on follow-up imaging *n*=11)	
Time from RAI to follow-up	9-40 (months) *n*=102	15.2±5.5 months
Dose I-131	29.8-206 (mCi) *n*=105	104.9±53.4 mCi
Age	18-79 (year of), *n*=107	49.8 (year of)±17.17 year
Prior surgery	TT *n*=95, ST *n*=9 *n*=104	-
Prior thyroid disease/relevant clinical history	Hashimoto's Thyroiditis *n*=9, toxic multinodular goiter *n*=1, pheochromocytoma *n*=1, NOS *n*=96	
Pathology diagnosis of primary tumor	Classic follicular cell PTC *n*=4, *n*=1 Tall cell variant, *n*=1 Hurthle cell, *n*=99 follicular cell PTC NOS	
Primary tumor spread staging at surgery	Extension beyond the thyroid=41, Internal to the gland=61, cervical LN positive=10	
Disease focality at surgery	LN surgical dissection=44/91=48.4%, 42.6/91=52.6%	

TT: Total thyroidectomy; ST: Subtotal thyroidectomy; PTC: Papillary thyroid carcinoma; NOS: Not otherwise specified; LN: Lymph node

Table 2: Clinical features and associations with biochemical treatment failure post-RAI

Clinical feature	Variable Range, *n*	*P*
Time from RAI to f/u	12–28 months, *n*=102	>0.22
Post-RAI Tg antibody	<1.0-3.2 IU/ml, *n*=101	0.22
I-131 dose administered	29.8-200.0 mCi, *n*=102	0.0147 (>160 mCi) RR=2.12
Pre-RAI Tg	0-58560 ng/ml, *n*=31	<0.0001 (elev) RR=2.26
Age	24-77 years old, *n*=107	0.192
Sex male/female	Male *n*=34, female, *n*=73	0.433
Time from Surgery to RAI	1.0-11.0 months, *n*=102	0.064 (>1.0 month) RR=0.78
Pre-RAI Tg antibody	1.0-6.0 IU/ml, *n*=31	0.011 (elev) RR=1.82
Post-RAI Tg[a]	<1-1516 ng/ml, *n*=105	N/A
Previous thyroid disease	Hashimoto's, TMNG, *n*=105	0.22
Thyroidectomy	Subtotal, total, *n*=104	0.45
Differentiated thyroid carcinoma type	Follicular, papillary, follicular variant, *n*=104	0.22
Size of primary tumor	0.6->5 cm, *n*=104	0.057 (≥4.5 cm)
Extent at surgery	Localized, extragland extent, lymphovascular or muscle invasion *n*=102	0.0135 RR=1.914
Lymph node involvement at surgery	Yes/no, *n*=91	0.16
Focality at surgery	U=33, M=61, *n*=94	0.026 multifocal RR=1.73
Total feature categories=16		

[a]By definition, treatment failure is elevated Tg levels following RAI. Results were the same with 2, 3, 4, 5, 10, and 20 of the most important features chosen before logistical regression performed. IU: International unit, U: Unifocal, M=Multifocal, RR: Relative risk of treatment failure, elev: Elevated lab value, N/A: Not applicable, since elevated serum Tg post-RAI is by definition treatment failure, RAI: Radioiodine, TMNG: Toxic Multinodular Goiter

categorical data, a random forest classifier was utilized and with the noncontinuous nature of the data, we implemented ANOVA F-values to look for the importance of each feature within the overall classification scheme.[9] Of those clinical features closely associated with treatment failure, a cutoff *P* value of 0.05 was considered to be statistically significant.

RESULTS

A total of 107 patients met the criteria to be included in this study, with an average age of 49.8 (±17.2) years old (ranging from 18 to 79 years old). Of these, 46 patients had treatment failure after the first dose of radioiodine as defined by biochemical serum markers and/or on imaging [Table 1]. The mean time from RAI to follow-up was 15.2 (±5.5) months and the mean dose of radioiodine prescribed was 104.9 (±53.4) mCi [Table 1]. Using a machine-learning algorithm from Sklearn we analyzed the clinical dataset to discern which factors were associated with treatment resistance.

First, following surgery but before RAI, if the patient was found to have elevated serum levels of Tg and anti-Tg antibodies, then this was more likely to be associated with treatment failure ($P = 0.011$) with a relative risk (RR) of 1.82 [Table 2 and Figure 1]. Other associated factors with clinical treatment resistance include multifocal disease involvement within the gland ($P = 0.026$, RR = 1.73) and advanced stage of disease presentation at surgical resection (lymph node involvement, $P = 0.0135$, RR = 1.91),

both of which were found to be significantly associated with treatment failure [Table 2 and Figure 1]. Finally, a prescribed dose of I-131 over 160 mCi was associated with treatment failure ($P = 0.0147$, RR = 2.12) [Table 2 and Figure 1]. Since the prescribed dose usually follows from the clinical stage or presentation at surgery, I-131 doses higher than 50–100 mCi usually reflect a more advanced disease state.[2] Taken together, these patient profile features reflect a more aggressive subset of tumor types and thus a higher likelihood for treatment failure. Interestingly, we also observed that if the patient was administered radioiodine at or within 2 months of the primary surgical treatment of the disease, there were slightly more patients who went on to develop treatment failure with RAI than those who did not (total number who failed treatment by 2 months; $n = 25$ versus total number with successful treatment; $n = 24$). This relationship however was not statistically significant [$P = 0.064$, Figures 1 and 2]. This is in contrast to a similar (but not the same) type of study which demonstrated increased rates of successful RAI on patients who waited 1 month or less between surgery and RAI.[10]

We looked at factors affecting treatment failure which were determined by imaging as well as from biochemical evidence. The number of patients with metastasis seen on whole-body imaging at follow-up (planar whole-body postradioiodine scans or by 18F-FDG PET/CT) with or without biochemical evidence of post-RAI treatment failure was lower than those with primarily biochemical evidence of treatment failure as shown in Table 1 ($n = 11$ with treatment failure evidence primarily by imaging versus $n = 35$ with primary biochemical evidence of treatment resistance from the total of 107 patients).

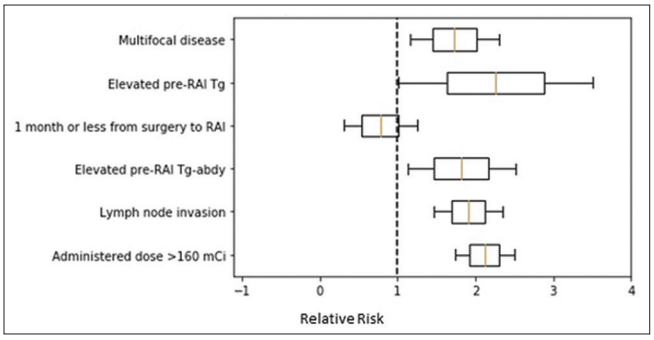

Figure 1: Relative risk of initial radioiodine treatment failure associated with specific patient clinical features. Whiskers denote the 95% confidence interval

DISCUSSION

A recent article outlining the importance of patient risk restratification and the utility it has for patient management describes a risk stratification system based on the 8th Edition of the American Joint Committee on Cancer tumor node metastases (TNM) staging system.[11] This system would better reflect the biological nature of thyroid cancer with the most important prognostic risk factors being the age at diagnosis, presence of distant metastasis, and extrathyroid extension. There is increasing clinical support for a patient risk restratification scheme with RAI treatment which better captures the patient-specific disease state and is reflected in improved outcomes.[11] In light of these proposed patient restratification systems, the factors we determined for treatment resistance can be utilized clinically.

The results of our study shed light on important clinical features when stratifying patients to receive therapy with RAI. Some of the clinical variables which we found associated with initial treatment failure agree with the previous literature looking at patient factors with RAI treatment failure.[1,3,12] In these studies, disease multifocality (diagnosed by surgical pathology) and large tumor size (>1 cm) at surgical resection were statistically significantly associated with treatment resistance such as was seen in a recent retrospective previous study looking at RAI treatment outcomes within a Filipino patient population.[3,13] This study however only

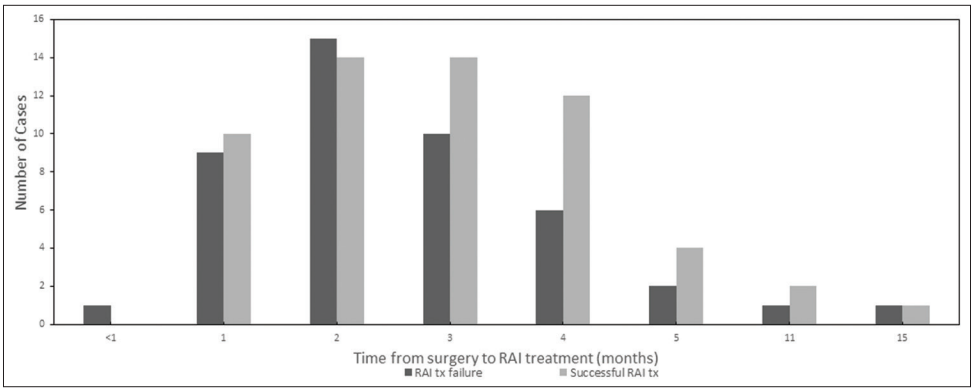

Figure 2: The number of cases of initial radioiodine treatment failure (dark gray bars) and successful RAI treatment (light gray bars) following thyroidectomy. Number of cases of each clinical response are displayed according to the number of months between surgical resection and RAI treatment

Table 3: Clinical features and associations with post-RAI treatment failure comparison using multivariate logistical regression with IBM SPSS Statistics 27 versus a machine learning algorithm implemented in Sklearn from Python v2.7.

Clinical feature	*P*	
	SPSS (IBM) multivariate logistic regression	Sklearn (Python)
Time from RAI to f/u	0.453	>0.22
Time from surgery to RAI	0.785	0.064
Pre-RAI Tg antibody	0.282	
Post-RAI Tg antibody	0.266	0.22
I-131 dose administered	0.165	0.0147
Pre-RAI Tg	0.997[a]	<0.0001
Post-RAI Tg		
Age	1.00[a]	0.192
Sex male/female	1.00[a]	0.433
PMHx		0.22
Surgical resection	1.00[a]	0.45
DTC type	1.00[a]	0.22
Tumor size	0.993-0.997	0.057
Tumor focality at surgery	0.042 (multifocal)	0.026 (multifocal)
Tumor extent at surgery	0.037	0.0135
Ln involvement at surgery	0.128	0.16

[a]No statistically significantly association $P>0.05$. DTC: Differentiated thyroid cancer, RAI: Radioiodine

looked at patients in a specific ethnic cohort. Although our patient cohort was smaller in number than this study, it was not limited to a specific ethnic cross section of the public. However, similar to this prior work, we also found that tumors which had spread to involve lymph nodes initially at the time of surgery were more likely to be implicated in RAI treatment resistance. These cases likely involve disease with a more aggressive initial profile and thus would be harder to treat using only a single dose of I-131. Interestingly, in a previous study, there was no reduction in disease recurrence when RAI was added to the treatment protocol in treating patients who had initial multifocal disease.[14]

Another similar study, matching closer in method to ours, looked at treatment outcomes in DTC following RAI, using multivariate analysis to assess independent risk factors for treatment resistance.[10] The authors found that age ≥45 years old, tumor size ≥2 cm, and a multiple number of nodules with disease (multiple foci of disease carried a higher risk) and more advanced TNM Stage (III-IV) all of which were associated with a statistically significant resistance to RAI ablation ($P < 0.05$).[10] This study however differs from ours in that they grouped patients into those that received 2, 3, or 4 consecutive doses of I-131, whereas we looked only at first-time treatment failure with RAI. The risks identified for treatment resistance in this previous study which were in accordance with the results of our study were multifocality of tumor at surgical resection and local tumor invasion (reflected in a higher TNM stage). Unlike the study by Cao *et al*., in our study age was not statistically significantly associated with resistance, however nearly all cases of resistance in our patient cohort showed a tumor size >0.6 cm (0.6–5 cm, $n = 104/107$) similar to findings from these other previous studies.

In addition, similar to these studies we found that a greater initial tumor size and patients who were given a higher initial RAI dose (prescribed for a higher clinical stage) were both associated with treatment failure [Table 2] also likely reflecting a more aggressive biological disease profile. Specifically, patients who were given a larger dose of I-131 initially reflected a more aggressive or advanced disease profile and showed a propensity towards treatment failure [$P = 0.0147$, RR = 2.12 Table 2 and Figure 1]. Along these lines, it is not surprising that an association was seen with patients who failed initial treatment and those who had elevated serum anti-Tg antibodies denoting residual disease [Table 2].

Of the patients with recurrent disease primarily by imaging at follow-up, a slightly greater number had elevated postsurgery (pre-RAI) Tg antibody levels ($n = 6$ elevated Tg levels vs. $n = 4$ normal serum levels). Of these patients with treatment failure assessed only by imaging, two patients had features of initially aggressive disease as depicted in the 2015 ATA guidelines.[2] One patient had treatment failure with normal post-RAI Tg, serum levels however the post-RAI Tg antibody levels were elevated and on follow-up imaging, there were supraclavicular, axillary, and mediastinal lymph node metastases which showed activity on 18F-FDG PET/CT exam. The primary tumor was large (4 cm) and multifocal involvement at surgery as well as extra-capsular extension and metastatic lymph node involvement was seen. Many of the FDG-avid lymph nodes which were not seen on post-RAI whole-body planar images however were confirmed as metastases on biopsy. In addition, this patient had a scapular osseous metastasis which was not seen on the whole-body post-RAI scans but was identified first on plain radiographs. This also turned out to be metastatic disease on biopsy. The second patient also showed a large multifocal primary tumor (size-4 cm) with angiovascular invasion at surgery. Post-RAI Tg and Tg antibody levels were normal, however a follow-up 18F-FDG PET/CT showed indeterminant esophageal activity, no biopsy was performed however in this case as it was felt to be unnecessary.

A finding which was surprising and novel to our knowledge was that a shorter time (<8 weeks) from surgery to

RAI treatment was weakly associated with treatment failure [Figure 2]. Although not statistically significant, we thought that this may reflect a suboptimal postoperative state for administering radioiodine therapy despite stimulation with rhTSH. An inflammatory environment or state of initial postsurgical healing may hamper the effective utilization of radioiodine therapy within the thyroid bed. These results are in contrast to those from a study by Cao *et al*. which found more patients had successful ablation at 1 month or less following surgery. Instead, we found a slightly higher number of patients with first-time treatment failure at 1 month or less following surgery. Successful remnant ablation was defined by the authors of that previous study as undetectable Tg or absence of disease evidence on follow-up radioiodine scans.[10] One possible explanation for this discrepancy between their study and ours is that in this previous study patients were given two or more doses of RAI, and repeated I-131 given in rapid succession within a month may have a boosted effect of accumulated cell damage from repeated radioiodine in a short interval of time. Finally, we explore the possible explanation that there could be a component of patient selection bias affecting our results such that more advanced or aggressive cases were scheduled for RAI sooner following surgery.

We compared our results from the machine learning algorithm with the commercially available statistics software package SPSS Statistics from IBM (version 27, 2020). We found similar results in terms of which clinical features were significantly associated with resistance to treatment (Table 3). These included tumor extent (P=0.037) and tumor focality (multifocal P=0.042) at surgery both of which were associated with resistance to RAI. Additionally, there were differences between what SPSS and the machine learning program picked out as being associated with treatment resistance. The pre-RAI Tg and Tg antibody levels as well as the I-131 dose administered were found to be associated with treatment resistance only with the machine learning analysis (Table 3). Part of the difference in the output of these two programs may be attributable to the methodologies used by each one. Although beyond the scope of this article, the methods used by Sklearn involve random forest tree classifiers whereas, the multivariate regression analysis by SPSS uses a method of ordinary least squares to find the contribution of each variable to the overall model fit of the data. In our dataset, the relationships between variables may be better depicted using one method versus the other one.

Some of the limitations of our study are that it is a retrospective study without matched controls. Only patients with follow-up serum Tg and anti-Tg levels and/or radioiodine imaging were included which may lead to a selection bias in our cohort. Our patient study size was modest ($n = 107$) since this was a single-center study and could be subject to sample-size limitations as well as institution-specific protocol effects such as selection and/or recall bias. The study size also could have effects on the machine learning algorithm as the training set would be smaller and more prone to data overfitting. We tried to use the simplest decision tree model algorithm as possible to work with our smaller dataset.[9] To help further address these issues, we implemented data-shuffling and cross validation to ensure that the algorithm was trained and tested in a robust fashion.[9] Finally, the machine learning algorithm we used from Sklearn has not been validated on a clinical dataset taken from the medical record like the one used in this study.

CONCLUSION

Identifying factors associated with reduced treatment efficacy is paramount in improving the delivery of clinical care to patients for radioiodine therapy. This type of study is important in addressing some of the shortcomings in the management of patients with DTC following surgical resection. By utilizing a machine learning multivariate data analysis technique, we found relevant clinical variables which may help restratify patients who are more resistant to initial RAI therapy. With this in mind, better management of these patients in the postoperative state can be realized. By implementing these results, improved clinical outcomes and better quality of life for patients treated with RAI can be achieved.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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