

Adjuvant radioiodine treatment in patients with thyroid cancer – current recommendations

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Radioactive iodine therapy (RAI) has been used in patients with differentiated thyroid cancers (DTC) for many decades. However, many changes in thyroid cancer treatment have been introduced for the last decade worldwide, mainly a tendency to deescalate both surgical and adjuvant treatment has been observed. This work summarizes current Polish guidelines for adjuvant radioiodine therapy compared to American Thyroid Association recommendations.

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Radioactive iodine (RAI) has been used for the postsurgical treatment of differentiated thyroid cancer (DTC) for over 50 years. Its therapeutic application in DTC is related to the ability of thyroid cells (both normal and cancerous) to actively capture iodine, including RAI, which is a β radiation emitter [1]. The incorporation of RAI into a thyrocyte cell leads to the formation of free radicals that damage the DNA structure and contribute to cell death or loss of its growth and division potential. For many years, radioiodine treatment was routinely recommended as an adjunct to surgery regardless of the disease recurrence or death risk.

The last decade has introduced many changes related to DTC treatment. With the development of new diagnostic methods, such as thyroglobulin (Tg) measurement or ultrasound examination, as well as better understanding of the biology and natural history of DTC, routine post-surgical radioiodine treatment has been questioned. A tendency to deescalate both surgical and adjuvant treatment has been observed [2]. However, the targets of adjuvant ¹³¹I have remained unchanged and include the following:

- ablation of residual normal thyroid tissue, which may facilitate surveillance,
- ‘adjuvant therapy’ due to a potential tumoricidal effect on residual microscopic RAI-avid disease,
- the possibility of detection of unknown local or distant metastases in a post-treatment whole-body scan.

While all the above targets are important, the ultimate endpoint of postsurgical ablation is to minimise DTC recurrence and death, primarily by eliminating residual normal thyroid tissue or residual microscopic disease.

In patients with structural disease, particularly in patients with non-resectable disease or after a non-radical operation (R2) or with distant metastases, radioiodine therapy is not adjuvant treatment. In these cases, the target of radioiodine therapy is complete disease remission or palliative intension. There are no indications for radioiodine treatment in patients with anaplastic or medullary thyroid cancer.

Of note, treatment recommendations for DTC radioiodine therapy have changed over time and vary among countries. While American Thyroid Association (ATA) guidelines have become

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more and more restricted regarding the use of radioiodine, other countries, including Poland, are more open to recommending radioiodine therapy [3–5]. The main reason for this discrepancy is the lack of prospective randomised trials in DTC radioiodine treatment. Outside the radioiodine-refractory DTC setting, only two prospective randomised trials have been published [6, 7]. They are, however, related to the preparation for RAI therapy or RAI activity rather than to the indications for such therapy.

Eligibility for adjuvant ¹³¹I treatment in DTC is mainly based on a 3-stage recurrence risk classification (Tab. I) developed by the ATA [2]. The TNM classification alone is no longer sufficient and hence a detailed histological assessment is necessary. It should include information related to the size of the primary lesion, multifocality, histological subtypes of the cancer, the presence and the extent of the extrathyroid infiltration, angioinvasion and the assessment of the number and the diameter of lymph node (micro/macro) metastases. In the future, the diagnosis of the molecular status of the tumour (i.e. the presence of the mutation of increased risk of unfavourable disease course such as *BRAF* or *TERT*) may be necessary. However, currently it is not routinely considered at the time of patient eligibility for adjuvant treatment. Other significant factors for such therapy also include the measurement of postoperative Tg concentration.

Although the ATA recurrence risk scale (Tab. I) was accepted in Europe and Poland, its interpretation is different compared to the USA, particularly in patients from the intermediate recurrence risk group [5]. Both Polish and American guidelines stress the necessity of adjuvant radioiodine treatment in patients from the high risk group in whom histological findings revealed extrathyroid infiltration (pT4), the diameters of metastases ≥3 cm and angioinvasion of more than 4 vessels in follicular thyroid carcinoma or if high postoperative concentration of Tg is found [2, 4].

Adjuvant radioiodine therapy can be abandoned in patients from the low risk group in case of papillary thyroid cancer (pT1a) without other negative risk factors, which is consistent with European and American guidelines (Tab. II). However, in other advancement stages, eligibility for the extent of surgery and adjuvant radioiodine therapy is open to debate.

According to the ATA 3-stage recurrence risk classification, patients with lymph node micrometastases (<2 mm in diameter) whose number does not exceed 5 are included in the low risk group and radioiodine therapy is not routinely recommended. However, Polish guidelines recommend adjuvant RAI treatment in all patients with lymph node metastases irrespective of their diameter, number or location (pN1a, pN1b) (Tab. II, III).

According to the ATA, patients staged pT1b-T2N0 are included in the low risk group and in this case the ATA recommends lobectomy without adjuvant ¹³¹I treatment.

Currently in Poland, lobectomy is only performed in patients staged cT1aN0M0, as opposed to ATA recommendations [4]. In Poland, as in other European countries, patients staged pT1b-T2N0M0 receive adjuvant radioiodine treatment considerably more often.

Obviously, one of the reasons for such management is the different extent of surgical treatment (total or near-total thyroidectomy), the different courses of the disease, depending on the region of the world and the very good results of such management reported in European countries.

According to the Polish recommendations, adjuvant radioiodine therapy may be abandoned in patients staged pT1b-T2N0M0 if negative prognostic factors (e.g., aggressive histological subtype or angioinvasion) were not found postoperatively and the potential benefits of such management outweigh the risk of recurrence [4].

Table I. 3-stage recurrence risk classification of differentiated thyroid cancers based on the 2015 American Thyroid Association Guidelines [2]

Low risk group	Intermediate risk group	High risk group
<p>Papillary thyroid cancer with all of the following:</p> <ul style="list-style-type: none"> – no local or distant metastases; – total macroscopic tumour resection; – no extrathyroid extension; – no aggressive histology of tumour (e.g., tall cell, hobnail variant, columnar cell carcinoma); – no vascular invasion; – clinical N0 or <5 pathologic N1 micrometastases (<0.2 in largest dimension); – if ¹³¹I is given, there are no RAI-avid foci outside the thyroid bed on the first posttreatment whole-body scan. <p>Intrathyroidal, well differentiated follicular thyroid cancer without capsular or vascular invasion or minimal (<4 foci) vascular invasion.</p> <p>Intrathyroidal, papillary microcarcinoma, unifocal or multifocal, including BRAFV600E mutation.</p>	<ul style="list-style-type: none"> – microscopic invasion of tumour into the perithyroidal soft tissues; – aggressive histology; – papillary thyroid cancer with vascular invasion; – clinical N1 or >5 pathologic N1 with all involved lymph nodes (0.2–3 cm in dimension); – multifocal papillary microcarcinoma with extrathyroid extension and the presence of BRAFV600E mutation; – if ¹³¹I is given, there are RAI-avid foci outside the thyroid bed on the first posttreatment whole-body scan. 	<ul style="list-style-type: none"> – gross extrathyroid extension; – incomplete tumour resection; – distant metastases; – postoperative serum thyroglobulin level suggestive of distant metastases; – pathological N1 with any metastatic lymph node ≥3 cm in largest dimension; – follicular thyroid cancer with extensive vascular invasion (>4 foci).

Table II. Comparison of recommendations for adjuvant radioiodine treatment in patients from the low risk group based on Polish and American recommendations [2, 3]

Advancement		Strength of recommendation	ATA 2015 guidelines	Polish 2018 guidelines
T1a N0 (x) M0 (x)	lesion ≤1 cm unifocal multifocal	strong weak	no no	no no
T1b, T2 N0 (x) M0 (x) micro N1 M0 (x)	lesion(s) of 1–4 cm with no lymph node metastases or with the presence of lymph node micrometastases, with no distant metastases and with no other negative prognostic factors found in histological examination	weak	selectively	therapy can be abandoned after the assessment of postsurgical treatment (not applicable to patients with N1)

Table III. Comparison of recommendations for adjuvant radioiodine treatment in patients from the intermediate risk group based on Polish and American recommendations [2, 3]

Advancement		Strength of recommendation	ATA 2015 guidelines	Polish 2018 guidelines
T3 N0 (x)	lesion >4 cm	weak	consider	yes
T3 N0 (x)	extrathyroid extension	weak	consider/rather yes	yes
T1–3 N1a	central lymph node metastases	weak	consider/rather yes	yes
T1–3 N1b	lateral lymph node metastases	weak	consider/rather yes	yes

Similarly, differences are also noted in terms of recommendations for adjuvant therapy in patients from the intermediate risk group (Tab. III). In Poland, these patients are routinely qualified for ¹³¹I treatment, while in the United States abandonment of RAI treatment is permissible.

Eligibility for ¹³¹I adjuvant treatment is related to time after surgery and thyroid remnant volume. Radioiodine treatment should be performed at the earliest about 4 weeks postoperatively when the wound has healed, the postoperative oedema has resolved, and the Tg level has decreased. According to the Polish recommendations, therapy should be performed within 9 months after surgery, and when this period exceeds 9–12 months, the treatment is considered delayed. Indications for adjuvant radioiodine treatment 12 months after surgical procedure is questionable [4].

Large thyroid remnants (>1 ml on either site of the thyroid bed) are relative contraindications for radioiodine adjuvant treatment, since with large thyroid remnants treatment success rate is worse. Higher or repeated RAI activities are necessary, which results in increased RAI therapy-related risks [4].

A high level of thyroid stimulating hormone (TSH) is essential for RAI uptake by thyroid cells. Traditionally, a high level of TSH has been achieved by withholding thyroxine therapy for 4–6 weeks after surgery. As a result, hypothyroidism can affect the quality of life of patients and lead to the imbalance of several biochemical parameters, particularly in the elderly. Recombinant human TSH (rhTSH) was developed to facilitate RAI application without withholding thyroxine. In most Polish

radioiodine treatment centres, rhTSH is the preferred method of TSH stimulation. Therefore, there is no need to delay L-thyroxine therapy in patients after thyroid surgery.

To conclude, in Poland postoperative radioiodine therapy is given to patients:

- a) from the high and intermediate risk groups
- b) from the low risk group if:
 - lymph node micrometastases are found in the postoperative histological examination,
 - an increased concentration of Tg is found postoperatively (stimulated Tg level >10 ng/dl),
 - iodine accumulation is observed outside the thyroid bed.

Conflicts of interest: none declared

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