Radionuclide treatment of metastatic disease in patients with differentiated thyroid carcinoma

Lečenje metastatske bolesti radionuklidom kod bolesnika sa diferenciranim karcinomom tiroideje

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Introduction

In general, the therapy of differentiated thyroid carcinoma (DTC), includes initial treatment and follow-up of patients. Nowadays, there is no universal accepted consensus regarding initial treatment of DTC patients. Several countries have their own guidelines and recommendations for treatment of DTC 1–5. Beside all controversies, mostly accepted recommendation regarding initial treatment of DTC includes total or “near” total thyreoidectomy followed by the therapy with radioactive iodine (131I). Radioiodine ablation of postoperative thyroid remnants is usually recommended in all DTC patients regardless their stage (low or high risk of cancer-specific mortality and risk of relapse), due to easier monitoring of thyroglobulin (Tg) 6. Thyroglobulin is a glycoprotein that is produced by normal or neoplastic follicular thyroid cells. In the absence of thyroglobulin antibodies (TgAb), undetectable Tg after the thyroid stimulating hormone (TSH) stimulation is a valid parameter of remission and the absence of metastases. On the other hand, detectable or increasing Tg during follow-up indicates the appearance of metastatic disease. After radioiodine ablation, a life-long suppressive therapy with L-thyroxine should be prescribed to all DTC patients. Rarely, a palliative therapy including external beam radiation therapy and chemotherapy is recommended 7.

After the initial treatment, all DTC patients should be monitored life long, with the aim to detect persistent disease or recurrence. Each check-up should include laboratory analyses (thyroid hormones, TSH, Tg and TgAb) and ultrasonography of the neck. The result of diagnostic whole-body scintigraphy (WBS) with 131I (131I-WBS) is influenced by thyroid carcinoma affinity to accumulate 131I in the presence of high concentration of TSH achieved by one-month L-thyroxine withdrawal or with intramuscular application of human recombinant TSH 7. Whole-body scintigraphy is routinely performed as a routine check-up (a year after the radioiodine ablation), and thereafter in cases suspected for recurrence only 8. Magnetic resonance imaging (MRI) and computed tomography (CT) are useful for detection of neck and mediastinal metastases 9. Magnetic resonance is useful especially in non-iodine-avid and mediastinal metastases 10. Fluorodeoxyglucose (18F-FDG) positron emission tomography fused with computed tomography (18F-FDG-PET/CT) is a modern diagnostic procedure that is important in detection of non-iodine-avid metastases 11. Computed tomography is useful in visualization of small lung metastases, but is rarely performed due to iodine contrast interference with iodine therapy 12.

Local and regional metastases in differentiated thyroid carcinoma patients

Local recurrence and/or regional neck metastases usually appear during the first years of follow-up in approximately of 5%–20% DTC patients. Regional neck metastases represent about 60%–75% of all neck metastases. They are usually detected by neck ultrasound (in about 94% of cases), or by increased Tg levels or WBS (in 50% of cases) 13. However, these recurrences are not palpable if they are soft, small or located in a central neck compartment or behind the great neck vessels. Metastatic neck lymph nodes appear at ultra-
sound as round, hypoechoic, with microcalcification and cystic components, hypervascularized at Doppler ultrasound which can detect metastatic lymph nodes in early stage of disease if they are a few millimeters sized only. Fine needle aspiration (FNA) of lymph node suspicious of recurrence is important in detection of regional metastases, since Tg determination in the aspirate increases accuracy of cytologic report. The Tg serum level is not detectable in about 20% of patients with isolated lymph node metastases on L-thyroxine therapy. Thyroglobulin level remains undetectable after TSH stimulation in approximately 5% of these patients. Whole body scintigraphy detects metastases in about 60%–80% of patients with clinical neck lymph node recurrences (Figure 1). Mediastinal lymph node metastases are usually combined with distant lung metastases. Recurrences in soft tissues or invading aero-digestive tract appear in less than 10% of all neck metastases.

The most important treatment of locoregional recurrences is surgical removal of metastatic tissue. A mediastinal dissection with additional radioiodine therapy should be performed in case of bulky mediastinal metastases (even in the presence of micrometastases of the lungs). The best effect of \(^{131}I\) therapy is obtained when is a diameter of metastatic lymph nodes is less than 1 cm. Some authors suggest surgical treatment as additional procedure after the \(^{131}I\) therapy as initial treatment of recurrences. External beam radiation therapy is recommended only in patients with non-iodine-avid metastases, those with incompletely surgery and patients with invasion of aero-digestive tract and soft tissue. A combination of external radiation and chemotherapy (doxorubicin in small doses of 10 mg/m\(^2\) weekly) is suggested in extensive and nonoperable recurrences.

Tubiana et al. reported the ten-year survival rate of 62% in DTC patients with local and regional recurrences. Distant metastases appear approximately in 27% of DTC patients; metastases presented at the time of diagnosis (early metastases) occur in 9% of them, while metastases which appear during the course of disease (late metastases) occur in 18% cases. According to our results, distant metastases appear in 21.2% of DTC patients; the frequency of early distant metastases is 8.5%, while late distant metastases appear in 7.02%. Early metastases are more frequent in papillary carcinomas, while late metastases occur more often in follicular carcinomas. Appearance time of distant metastases does not significantly affect disease-specific survival (DSS) of DTC patients.

Patients with high risk for distant metastases appearance are younger than 16 years, older than 45 years, those with histological subtypes of papillary carcinoma (tall cell, columnar cell, diffuse sclerosing) and follicular carcinoma (widely invasive and poorly differentiated), patients with bulky tumors, those with tumors extended beyond thyroid capsule and with nodal metastases, patients who underwent less extensive surgery than total or near total thyroidectomy, or those with no post-surgical administration of radioiodine ablation. Lung metastases are often combined with lymph node recurrences in central neck and mediastinal compartment (Figure 2). Papillary carcinomas usually extend lymphogenously to the lungs, while follicular carcinomas extend hematogenously to the lungs and bones. Distant metastases are usually located in lungs (57%), bones (24%), spine, pelvis, long bones, ribs, sternum, the base of the skull. One third of metastases in bones represent solitary bone metastases. Lung metastases associated with bone metastases occur in 16% patients, while metastases in liver, brain and skin appear in 3% of the patients.
Surgery should be the primary treatment of bone metastases. This treatment is not recommended if multiple lung metastases are present. Radioactive iodine is accumulated only in 2/3 patients with distant recurrences, but is able to destroy only a small tumor foci. Radioactive iodine is performed in activity ranged from 5.55 to 7.4 GBq in adults, every 6 months during the first 2 years, and thereafter annually until complete ablation of residual uptake on posttherapeutic $^{131}$I-WBS. Most patients are cured with cumulative activity of $\leq 18.5$ GBq. Even the fact that risk of secondary carcinoma and leukemia increases with higher cumulative activity of $^{131}$I, there is no limit for cumulative activity which can be performed in DTC patients with metastatic disease. If there is no uptake on posttherapeutic $^{131}$I-WBS, any further radioiodine therapy is useless (Figure 3). In these patients with so-called non-iodine-avid metastases, the exact localization of tumor deposits is possible with $^{18}$FDG-PET/CT (Figure 4).

![Posttherapeutic $^{131}$I-WBS](image1.jpg)

**Fig. 2 –** Posttherapeutic $^{131}$I-WBS (whole-body scintigraphy) shows regional recurrence in submandibular lymph node on the right side, and distant metastases in the upper mediastinum and both lungs (a – anterior view; b – posterior view)

![Posttherapeutic $^{131}$I-WBS](image2.jpg)

**Fig. 3 –** Posttherapeutic $^{131}$I-WBS (whole-body scintigraphy) of the patients with increased thyroglobulin serum level does not detect radioiodine uptake due to the presence of non-iodine-avid metastasis (a – anterior view; b – posterior view)
Complementary treatment of DTC includes external beam radiation therapy and chemotherapy. External radiation therapy should be performed in patients with non-operable and non-iodine-avid bone metastases. The metastases are located in vertebral column, near the base of the skull, sites where pathological fracture would cause a serious disfunction. In patients with iodine-avid bone metastases, a combined therapeutic protocol should be performed: radioiodine therapy followed by external radiation therapy, and afterwards additional $^{131}$I therapy should be applied in the interval of 3 to 6 months. The doses of radiation should be 30 Gy for 15 days, or 40 Gy for 28 days. Chemotherapy should be performed in patients with progressive recurrent disease refractory to $^{131}$I. In about 33% patients, there is a response to doxorubicin treatment (dose of 60 mg/m² every 3–4 weeks). Combination of doxorubicin-cysplatine has similar response, but greater toxicity. Treatment with interferon-α, interleukin-2 (alone or associated with doxorubicin) and somatostatin analogs usually result with no treatment response.

Complete remission (CR) after radioiodine therapy occurs in 33%–50% of DTC patients with distant metastases which accumulate radioiodine, and in 83% patients with normal chest radiography at the time of detection of recurrences, in 53% patients with micronodular lung metastases and in 14% patients with macronodular lung metastases.

Overall survival after 10 years from the detection of distant metastases is 25% to 40%. Prognostic factors such are iodine-avid distant metastases, younger age at the time of distant metastases diagnosis and metastases limited in extension indicate better prognosis. The study performed in our institution from 1977 to the end of 2005 included 75 DTC patients with distant metastases treated by $^{131}$I therapy. Our results suggest few prognostic factors which significantly affect the disease-specific survival (DSS) of DTC patients with distant metastases: age, histological type of the tumor and initial treatment. We found that the survival of DTC with distant metastases is significantly shorter in patients of 45 years or older than in patients below 45 years, with a highly statistically significant difference ($p = 0.0001$). According to the tumor histology, patients with papillary metastatic thyroid carcinoma have significantly longer survival than patients with follicular metastatic thyroid carcinoma ($p = 0.0138$). Our data also suggest that patients who underwent adequate initial treatment (including total or near total thyroidectomy followed by $^{131}$I therapy) show significantly longer survival compared to patients initially treated inadequately (nodulectomy, lobectomy, loboisthmectomy or subtotal thyroidectomy, alone or combined with $^{131}$I therapy, $p = 0.0351$). On the contrary, we detected that the gender of DTC patients with distant metastases has no influence on disease-specific survival ($p = 0.2046$).

The ability to accumulate $^{131}$I is also important prognostic factor. In our study, the probability of DSS in patients with iodine-avid metastases is 67% after 5 years, 55% after 10 years and 45% after 15 and 20 years, while DSS in patients with non-iodine-avid metastases is 18% after 5 and 10 years ($p = 0.0006$).

**Conclusion**

Patients with DTC should be adequately and optimally initially treated including total or “near” total thyroidectomy followed by radioiodine therapy. Those patients should be monitored lifelong in order to detect recurrences on time. The survival of DTC patients with distant metastases is short, but optimal treatment provides better quality of life.
REFERENCES


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