University of Groningen

Embolization Therapy of Bone Metastases from Epithelial Thyroid Carcinoma

De Vries, Margriet M.; Persoon, Adrienne C. M.; Jager, Pieter L.; Gravendeel, Joost; Plukker, John T. M.; Sluiter, Wim J.; Links, Thera P.

Published in:
Thyroid

DOI:
[10.1089/thy.2008.0066](https://doi.org/10.1089/thy.2008.0066)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2008

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

De Vries, M. M., Persoon, A. C. M., Jager, P. L., Gravendeel, J., Plukker, J. T. M., Sluiter, W. J., & Links, T. P. (2008). Embolization Therapy of Bone Metastases from Epithelial Thyroid Carcinoma: Effect on Symptoms and Serum Thyroglobulin. *Thyroid*, 18(12), 1277-1284. <https://doi.org/10.1089/thy.2008.0066>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Downloaded from the University of Groningen/UMCG research database (Pure): <http://www.rug.nl/research/portal>. For technical reasons the number of authors shown on this cover page is limited to 10 maximum.

Embolization Therapy of Bone Metastases from Epithelial Thyroid Carcinoma: Effect on Symptoms and Serum Thyroglobulin

Margriet M. De Vries,¹ Adrienne C.M. Persoon,¹ Pieter L. Jager,² Joost Gravendeel,³ John T.M. Plukker,⁴
Wim J. Sluiter,¹ and Thera P. Links¹

Background: Selective embolization therapy (SET) has been employed to treat a number of malignant tumors, but experience with its use in metastatic epithelial thyroid carcinoma (ETC) is limited. Here we report our experience with the effect of SET on symptoms and serum thyroglobulin (Tg) in patients with bone metastases from ETC.

Methods: This was a retrospective study of 13 patients with bone metastases from ETC who underwent 65 embolizations for bone metastases in 43 sessions. In the treated patients, symptoms considered related to bone metastases were compared before and about 4–7 weeks after the embolization session. Embolization sessions were excluded for analysis if concomitant therapy had taken place within 4–7 weeks before and/or after the session. Serum Tg concentrations were employed as an index of tumor debulking by SET. We attempted to estimate the influence of SET on survival time in patients with disseminated ETC who did, and an historical control group of patients with disseminated ETC who did not receive SET.

Results: After exclusion of 12 (of which 3 sessions failed) out of 43 sessions, clinical symptoms, such as pain, and neurological symptoms decreased after 17, increased after 6, and did not change after 8 procedures. In 43 sessions, 20 of which were excluded (including the 3 sessions that failed), serum Tg decreased after 14 and increased after 9. The median standardized survival time of the group that received embolization was not significantly different to that of the group that did not receive embolization.

Conclusions: Embolization therapy does not appear to improve life expectancy, but in selected patients can achieve palliation of pain, prevent neurological damage, reduce tumor burden, and give devascularization of the tumor before surgery.

Introduction

ALTHOUGH OVERALL SURVIVAL in patients with epithelial thyroid carcinoma (ETC) is excellent, patients with persistent disease have a life expectancy of approximately 60% of the normal residual life span (1). The challenge in treating this persistent disease is to improve survival and control symptoms such as pain and different neurological symptoms. Standard treatment consists of thyroidectomy followed by high-dose radioiodine and lifelong thyroid hormone suppression therapy. In cases of persistent disease, surgery and occasionally additional external beam therapy are used. Other treatments, including labeled octreotide, have limited results (2).

Selective embolization therapy (SET) for the treatment of bone tumors was first described by Feldman *et al.* in 1975 (3). Camille *et al.* (4) were the first to write about preoperative embolization therapy for thyroid carcinoma. They wrote about embolization of metastases from thyroid carcinoma before surgery in four cases with spinal or pelvic metastases.

Several case reports with embolization therapy in the treatment of thyroid cancer are described (5–10). Few reports, including one report written by our group, deal with embolization therapy for bone metastasis in thyroid cancer (11,12); others concern direct embolization of the primary thyroid tumor (13,14) or the use of embolization as a preoperative procedure (15–18). These reports indicated that some patients achieved a rapid reduction in pain and tumor burden. Barton

¹Department of Endocrinology, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

²Department of Nuclear Medicine, McMaster University Medical Centre Site, Hamilton, Canada.

Departments of ³Radiology and ⁴Surgery, University Medical Center Groningen, University of Groningen, Groningen, The Netherlands.

et al. (19) showed that embolization is generally an effective treatment for bone metastases of different primary tumors. It is known that embolization therapy together with anti-vascular therapy (Marimastat) has no additional effect for clinical symptoms (20).

Previous studies have shown that clinical improvement was not always concordant with tumor regression on imaging (12).

We report our experience with the effect of SET on symptoms and serum thyroglobulin (Tg) in patients with bone metastasis from ETC, and we investigate if SET has an additional value to life expectancy.

Materials and Methods

The University Medical Center Groningen is the major referral center in the northern part of The Netherlands for treatment of patients with ETC. The treatment regimen and follow-up were described earlier (21) and consisted of a total thyroidectomy and I-131 therapy, with Tg measurement under thyroxine suppression therapy after a negative post-therapeutic whole-body scan (WBS).

The patient group was consisted of 13 patients with disseminated ETC who received SET for their bone metastases to control pain, and/or to achieve tumor debulking, and in specific cases to obtain devascularization before surgery. An additional nonrandomized group of 87 patients with disseminated ETC who did not receive SET (No-SET group) was used to estimate the impact of SET on survival. Between 1996 and 2006 the 13 SET-treated patients underwent 65 embolizations in 43 sessions. Eleven of these patients had persistent disease after initial therapy, and nine of them presented with only bone metastases. The other two patients were in remission after initial treatment, but developed recurrent persistent disease with bone metastases. The SET procedures were executed after obtaining informed consent.

The 87 patients in the No-SET group were part of the large cohort that has been described earlier (1). Sixty-seven of these patients had persistent disease after their initial surgical and radioiodine treatment, and 20 patients developed recurrent disease after this initial treatment and did not have a second remission after the additional treatment.

Regarding terminology, an embolization session refers to several embolizations in one patient on the same day, and an embolization refers to one embolization procedure.

The success of embolization was evaluated by additional angiography after the embolization session. After 3–4 months the success of the embolization was measured by magnetic resonance imaging and computed tomography. Embolizations that were at least 60% complete were considered partially successful, and embolizations that were 100% complete were considered completely successful.

Completely and partially successful embolizations were included in the analysis unless there was concomitant therapy near the time of the procedure. In 43 embolization sessions during which 65 embolizations were administered, 48 embolizations were successful, 13 embolizations were partially successful, and 4 embolizations were not successful. To evaluate the effect of therapy (symptoms and Tg levels), no concomitant therapies in a period of 4–7 weeks before and after the embolization sessions were accepted for evaluation. Therefore, nine embolization sessions were excluded because

of concomitant surgery (four sessions and four embolizations), antivasular therapy (three sessions and eight embolizations), and I-131 therapy (two sessions and two embolizations). In eight other embolization sessions no Tg levels were available. Of the total 12 and 20 embolization sessions that were excluded, both contained the 4 embolizations executed in 3 sessions that failed. In sum, 23 embolization sessions were evaluable for Tg levels and 31 sessions for symptoms.

Persistent disease after initial therapy was defined as clinical evidence of thyroid cancer found at any visit after ablation. Recurrent disease was defined as tumor recurrence indicated by newly detectable Tg during suppression therapy or clinical evidence of disease detected by other technique. The characteristics of the SET and non-SET groups are given in Table 1. Both groups were compared for differences in survival. Most of the patients in the embolization group have follicular thyroid carcinoma and M1 tumors for metastases. For survival, both subgroups of patients were also compared separately with the same subgroup in the control group.

Laboratory methods

Serum Tg was measured by a commercially available radioimmunoassay (Cis Bio International, Gif-sur-Yvette, France), with a lower detection limit of 1.5 ng/mL. In cases of an undetectable serum Tg, the presence of Tg antibodies was evaluated by recovery of added standard Tg. Tg antibodies were considered to be absent if recovery was >85%. None of our patients had Tg antibodies.

After March 2004 the Tg-immunochemiluminometric assay was determined (the Nichols Advantage® Tg assay; Nichols Institute Diagnostics, San Clemente, CA), detection limit <0.6 ng/mL, and antibodies by the Nichols Advantage TgAb assay (Nichols Institute Diagnostics) with a cutoff value for TgAb positivity of 2 mIU/L were introduced (22).

Embolization technique

Before embolization, all the tumor-supplying vessels were visualized by diagnostic angiography. Embolization was performed during the same session. A no. 6 French (F) sheath was placed into the femoral artery, to facilitate catheter exchange. Then a 6 F guiding catheter (Boston Scientific, Natick, MA) was inserted proximal in the main tumor-feeding artery. With a microcatheter (Excel 14; Boston Scientific) a superselective microcatheterization of the tumor vessels was

TABLE 1. PATIENT CHARACTERISTICS

	Embolization group	Control group	p-Value
Sex: male/female	2/11	34/53	0.20
Age (±SD)	57.5 (±14.1)	60.7 (±15.7)	0.29
TNM classification			
N0/N1	13/0	44/43	0.005
M1/M0	11/2	23/64	0.0005
Histology (pap/foll/Hürthle)	0/12/1	43/30/14	0.0003

pap, papillar; foll, follicular; Hürthle, Hürthle cell carcinoma (patient number 10).

TABLE 2. ARTERIES TREATED WITH EMBOLIZATION THERAPY

<i>Site metastases^a</i>	<i>Embolized artery</i>
Patient 1	Embolized artery
1. Acetabulum(r)/os ischii/ramus superius ossis pubis	Internal iliac a.(r)
2. os ischium(r)/ramus ossis pubis(r)	Internal iliac a.(r) tumor branches/medial circumflex of femoral a.(r)
3. Acetabulum(r)	Not specifically mentioned
4. Relapse proximal and at the same height of known pelvis metastase(r) os ischium extended to medial backside of acetabulum and os pubis(r)	Internal iliac a.(r) (tumor branches)
5. os ischii(r)/sacrum/acetabulum(r)/os pubis	Medial and lateral circumflex of femoral a.
6. os ilium medial/sacrum/os ischii/upper part medial os pubis(r)	Internal iliac a.(r)
7. os ilium lateral	Gluteus maximus a.(r)
8. Ramus ossis pubis superior and inferior(l)	Internal iliac a.(l) (tumor branches)/tumor branch from retroperitoneal a. from external iliac a.(l)
9. Pubis ring	Separate branches from profunda femoris a.
10. os ileum(r)	Separate branches from profunda femoris a.
11. os pubis(l)	Separate branches from profunda femoris a.
Patient 2	Embolized artery
1. L4(r)	Lumbar spinal a. L3(r) and L4(r,l)
2. L4(l)	Lumbar spinal a. L3(l,r) (collateral a.) (right side by means of microcoil)
3. L4	Lumbar spinal a.(r) (collateral a.)
Patient 3	Embolized artery
1. Humerus proximal(l)	Lateral upper arm a. (tumor branches including coiling and separate branch)
2. os ilium lateral(r)	Internal iliac a.(r) (3 main branches)
3. Humerus proximal(l)	Axillaris a.(l) (tumor branches)
4. os ilium(r)	Internal iliac a.(r) (tumor branches)
Patient 4	Embolized artery
1. 6 th rib(l)	Costal a. 6 and 7(l) (including coiling)
Patient 5	Embolized artery
1. Th6, Th7(r)	Costal a. 7(r) (including coiling)
2. Th6, Th7(r)	Costal a. 6 and 8(r) (tumor branches)
3. Scapula	Costal a. 6 and 8(r) (tumor branches)
4. Th6, Th7(r)	Costal a. 7(r) (including microcoil)
5. Th6, Th7(r)	Costal a. 7(r) (including microcoil)
6. Pelvis/sacrum(l)	Lumbar spinal a.(l)
7. Th5(r)	Intercostal a. Th6(r)
Patient 6	Embolized artery
1. L3, L4(l)	Lumbar spinal a. L3(l) and L4(l)
2. L3, L4(l)	Lumbar spinal a. L4(l,r(proximal branch))
3. L3, L4(l)	Lumbar spinal a. L3(r) (tumor branches)
Patient 7	Embolized artery
1. os ilium(r) with infiltration in sacrum(r), underpart L5 lateral, acetabulum, os ischi	Internal iliac a.(r)/gluteal a. with collaterals to circumflex of femoral a. and the lowest lumbal a.(r)
2. Pelvis(r)	Internal iliac a.(r)(including microcoil)/circumflex of femoral a. (tumor branches)
3. Pelvis(r)	Internal iliac a.(r) (3 branches including coiling)
4. Pelvis(r)	Internal iliac a.(r) (collateral tumor branches including microcoil)
5. Pelvis(r)	Lateral circumflex of femoral a.(tumor branches)/ internal iliac a.(r) (tumor branches)
6. Pelvis(r)	Internal iliac a.(r)
7. os ilium lateral(r)	Internal iliac a.(r)
8. Sacrum medial(r)	Internal iliac a.(r)
9. os pubis medial/cranial(r)	Internal iliac a.(r)
10. os ilium(l)	Internal iliac a.(l)
11. os ilium(r) medial/cranial	Lumbar spinal a. L4(r)
12. Ilical(l) and at the SI joint(l)	Lumbar spinal a. L4(l)
Patient 8	Embolized artery
1. L2(r) (L1, L3)	Lumbar spinal a. L2(r)
2. L2, L3	Lumbar spinal a. L3(l,r) (including coiling)

(Continued)

TABLE 2. (CONTINUED)

<i>Site metastases</i>	<i>Embolized artery</i>
Patient 9	Embolized artery
1. Th10, Th11(r)	Intercostal a.(r) (including coiling)
2. Th10, Th11(l)	Intercostal a.(l)
3. Skull	Middle meningeal a. pre- and midbranch (tumor branches)
Patient 10	Embolized artery
1. L4(l)	Lumbar spinal a. L4(l) (including microcoils) (distal/proximal/tumor branches)
2. Pelvis(r)	Internal iliac a.(r) (including microcoil) (tumor branches)
3. L4	Lumbar spinal a. L4(l)/lumbal a.
4. L2	Lumbar spinal a. L2(l)/lumbalis a. (including coiling)
5. L3(l)	Lumbar spinal a.
6. os ilium(r)	Internal iliac a./proximal branch near internal iliac a.(r)/retroperitoneal branches at the transition of external iliac a. and femoralis communis a. (medial branch)
7. os ilium(r)	Retroperitoneal iliac circumflex a.(tumor branches)/internal iliac a.(r) (tumor branches)
8. L4(l)	Lumbar spinal a. L3(l)
9. L2(r)	Lumbar spinal a. L3(r) (tumor branches)
10. L4	Lumbar spinal a. L3(r) (tumor branches) and L4(l)
11. L3(r)	Lumbar spinal a. L3(r) (tumor branches)
Patient 11	Embolized artery
1. L3	Lumbar spinal a. L3(l,r(including coiling))
2. L3	Lumbar spinal a. L3(l)
Patient 12	Embolized artery
1. C4	Truncus costocervicalis(r), coiling bifurcation and vertebral a.(l)
Patient 13	Embolized artery
1. C5-C6	Truncus thyrocervicalis(l)

a, artery; r, right; l, left; L1–L5, lumbar vertebrae 1–5; Th5–Th7, Th10, Th11, thoracic vertebrae 5–7, 10, 11; C4–C6, cervical vertebrae 4–6.

performed. The tumor was embolized with repetitive small injections of polyvinyl alcohol foam particles of 150–250 μm (Contour emboli; Target Therapeutics, Fremont, NE). The treated site of the metastases and the embolized arteries are shown in Table 2. With additional angiography, the direct result of the embolization session was documented. For the detection of side effects, including the postembolization syndrome as flu-like symptoms or fever (11) and technical complications, all patients in whom embolization was performed were clinically observed during 24–48 hours.

Effect of therapy

The effect of the therapy was evaluated by clinical complaints such as pain, mobility, insensibility, and Tg levels. These data were collected from the patient charts retrospectively.

Clinical complaints of the local metastases were categorized as regression, stabilization, or progression. The clinical complaints before the embolization session were compared with those about 4–7 weeks after the embolization session.

Tg was measured 3 weeks before (range, 0–136 days) and up to 7 weeks after (range, 10–164 days) embolization during thyroid-stimulating hormone suppression. The individual standardized survival time was calculated as the ratio between the observed survival time of an individual and the median residual life span of the individuals with the same age

in the general population in the year of diagnosis as described earlier (1).

Statistical analysis

Differences in standardized survival were analyzed by log rank test. Continuous variables are given as mean with SD; differences were tested by Mann–Whitney *U*-test. Differences in prevalences were tested by chi-square test. Changes in subjective complaints and Tg concentrations were tested by sign-test. *p*-Values less than 0.05 were considered significant.

Results

Table 1 shows the characteristics of the SET and No-SET groups. More females were present in the embolization group, but age was comparable in both groups. The prevalence of distant metastases at diagnosis was significantly higher in the SET group ($p < 0.0005$) than in the No-SET group, and positive regional nodes were not present at diagnosis ($p < 0.005$). There were significantly more ($p < 0.0003$) follicular thyroid carcinomas in the SET group than in the No-SET group. Twelve patients in the SET group had follicular thyroid carcinoma; one patient (no. 10) had Hürthle cell carcinoma.

Table 3 shows the characteristics of individual patients, the number of embolizations, their locations, and additional

TABLE 3. INDIVIDUAL DATA ABOUT ADDITIONAL THERAPIES IN THE EMBOLIZATION GROUP

Patient number	Sex	Age ^a	T _x N _x M _x	Histology	No. of embolizations	Locations	Cum I-131 (mCurie)	Additional therapies
1	Female	60	T ₂ N ₀ M ₁	Follicular	11	1–11: pelvis	750	Pelvis: 50 Gy, pelvis 8 Gy
2	Female	60	T ₁ N ₀ M ₁	Follicular	3	1–3: L4	900	Paravertebral and L4: 24 Gy, corporectomy L4
3	Female	68	T ₃ N ₀ M ₁	Follicular	4	1,3: humerus, 2,4: ileum	750	Pelvis: 8 Gy
4	Female	46	T ₂ N ₀ M ₁	Follicular	1	1: 6th rib	900	Excision rib metastasis
5	Female	62	T ₂ N ₀ M ₁	Follicular	7	1: Th6, 2: Th7, 3: shoulder, 4: Th6, 5: Th7, 6: pelvis/sacrum, 7: Th5	600	Th. 6, 7, 8: 24 Gy, Sac: 24 Gy, Th5 25 Gy
6	Female	65	T ₂ N ₀ M ₁	Follicular	3	1–3: L3–L4	750	—
7	Female	40	T ₄ N ₀ M ₁	Follicular	12	1: pelvis and part L5, 2–12: pelvis	900	Pelvis: 50 Gy, L1–L3 30 Gy
8	Female	77	T ₂ N ₀ M ₁	Follicular	2	1–2: L2	450	Th. 12–L4: 30 Gy
9	Female	54	T ₂ N ₀ M ₀	Follicular	3	1: Th10, 2: Th11, 3: skull	650	Th. 5–12: 30 Gy, skull: 30 Gy, skull: 20 Gy
10	Male	35	T _x N ₀ M ₀	Follicular	11	1: L4, 2: ileum, 3: L2, 4: L3, 5: L4, 6: ileum, 7: ileum, 8: L4, 9: L2, 10: L4, 11: L3	640	L1–L5: 8 Gy
11	Female	52	T _x N ₀ M ₁	Follicular	2	1–2: L3	600	Corporectomy L3
12	Female	45	T ₃ N ₀ M ₁	Follicular	1	1: C4	450	Corporectomy C4
13	Male	83	T _x N ₀ M ₁	Follicular	1	1: C5/C6	150	Surgical C5–C6

^aAge: at initial diagnosis (from duration of illness).
T, tumor; N, nodes; M, metastases.

therapies. Eight patients in the SET group were locally treated with external beam therapy; five of these patients had this therapy before the embolization session. The mean time of external beam therapy before an embolization session was 10.5 months with a range of 1.5–20.5 months. Of the 13 embolizations that partially succeeded and the four embolizations that failed, external beam therapy was not given before embolization.

Figure 1 shows the angiogram made before the embolization session. In Figure 2A and B the situation before and after embolization of the left side is visible after finishing the right side of L3. Indications for embolization were tumor debulking before I-131 therapy (42.5%), preventing neurological damage (35%), diminishing complaints of pain (45%), and embolization before debulking surgery (10%). In total the percentages are more than 100% because some embolization procedures had more indications.

Pre- and post-SET symptomology in patients with successful embolizations

Symptoms of patients comprised pain and neurological symptoms, like numbness, tingling, or radicular pain. Symptoms decreased during 17 sessions, were unchanged during 8 sessions, and increased during 6 sessions ($p < 0.01$). The duration of improvement after these 17 sessions had a mean duration of 8.1 months with a range of 0.2–36 months. The most effective embolizations were performed at the first session. Most of the patients of whom the symptoms were unchanged after the session did not have complaints before the embolization session.

FIG. 1. Angiogram before the embolization session of patient 11 (anteoposterior projection). Selective catheterization of the feeding lumbar artery on the left side shows a blush in the metastase of the 3rd lumbar vertebra (L3).

FIG. 2. (A) A sagittal T1-weighted image noncontrast enhanced of patient 11, showing a process in the third lumbar vertebra (L3) with destruction of the posterior wall of the corpus. (B) An axial T1-weighted image noncontrast enhanced, showing the same findings. Tumor extending into the pedicles bilaterally. Widening on the left side.

Tg levels

In 23 of the 43 embolization sessions Tg levels were evaluable. Before embolization Tg levels ranged from 18 to 18,200 ng/mL, and afterward from 13 to 37,400 ng/mL (Table 4). After the embolization, serum Tg levels decreased in 14

TABLE 4. Tg LEVELS BEFORE AND AFTER EMBOLIZATION SESSION

Patient	Tg level before embolization (ng/mL)	Tg level after embolization (ng/mL)
1	11,000	2375
	178	202
	18,200	16,800
	16,800	37,400
2	4365	2400
	18	13
3	246	102
	67	70
5	525	16
	1415	1730
6	155	250
	250	827
7	1240	379
	489	442
	1110	1098
8	97	45
	50	14
9	772	276
	214	198
10	685	1280
	6910	25,350
	5460	9200
11	65	17

Tg, thyroglobulin.

procedures (mean change, 1015 ng/mL) and increased in 9 procedures (mean change, 4932 ng/mL, not significant). The greatest changes in serum Tg after embolization were noted in patients with the higher serum Tg concentrations (Table 4).

Of the 14 patients who had a decrease in Tg level, 8 patients had symptomatic relief, 4 patients did not feel difference in their complaints, and 2 patients had an increase of symptomatic complaints. Of the nine patients who had an increase in Tg level, four patients had symptomatic relief, two patients did not feel difference in their complaints, and three patients had an increase of symptomatic complaints.

Survival time in SET and non-SET patients

The survival expressed as median standardized survival time was not significantly different between the SET group, which was 0.43 (95% confidence interval [CI], 0.24–0.63), and the non-SET group, which was 0.56 (95% CI, 0.39–0.74).

Comparison of the patients with follicular thyroid cancer separately showed no significant difference, 0.42 (95% CI, 0.04–0.80), in the survival between the patients with embolization therapy and the patients of the control group. Comparison of the standardized survival of the 13 patients from the embolization group with the 23 patients from the control group with M1 tumors also showed no difference, 0.42 (95% CI, 0.0–0.95).

Complications

During the first five embolization sessions no steroid coverage was added, and several minor complications occurred

(temporary hypotension, postembolization syndrome, and local edema). Afterward, prednisolone was given 30 mg daily during 2 weeks, and then was tapered in 2 weeks. No complications were seen in the following 38 embolization sessions.

Discussion

Our series illustrated that embolization therapy can achieve palliation of pain and prevent neurological damage in a substantial number of patients with bone metastases from epithelial cell thyroid cancer, but in contrast to radical surgical removal of bone metastases (23), embolization therapy does not appear to improve survival. Based on serum Tg measurements taken weeks after this therapy, it appears that more than half of treated patients achieved a reduction of tumor burden. Life expectancy, however, is probably not influenced by embolization therapy. The changes in serum Tg after embolization therapy were highly variable, but a decrease was noted more often than an increase.

When embolization therapy was successful or partially successful, in 61% there was a decrease of the serum Tg level. To minimize a possible long-lasting effect of other treatments, we used in our analysis only those embolization sessions for patients who had received no additional therapy 28–49 days before and for the same period after their embolization sessions. It should be noted that the half-life of Tg in the circulation is 4 hours to 4 days (24–26). Therefore, as serum Tg was measured at least 10 days after embolization therapy, it seems unlikely that serum Tg reflected acute necrosis of infarcted tumor tissue. Our data suggest that Tg is a weak indicator of tumor necrosis after embolization. Embolization therapy appears to be beneficial in two ways. First, it appears to improve the quality of life in some patients. This is particularly important because the survival of patients with metastatic differentiated thyroid cancer (DTC) is relatively long. This conclusion is also supported by the study of Eustatia-Rutten *et al.* (12). They noted that a substantial percentage of patients had improvement in clinical symptoms after embolization therapy, although some of these patients did not have tumor regression scored by Tg level and/or imaging. In another study of four patients, Smit *et al.* (9) noted dramatic relief of neurological symptoms after embolization therapy of vertebral metastasis from differentiated follicular thyroid carcinoma. In a third study of Van Tol *et al.* (11), there was improvement of symptoms in patients treated with embolization and radioiodine therapy, but this improvement was not significantly different compared to patients treated with radioiodine therapy alone. The present study is a larger one than our early preliminary study (11) of five patients with bone metastasis due to DTC. In that study, radioiodine therapy alone or radioiodine therapy combined with embolization therapy was used, and there was a significantly greater decrease in serum Tg in patients when the combination of embolization and radioiodine therapy was employed than radioiodine alone. In the current larger series we conclude that embolization therapy is beneficial in a substantial number of patients. In our patients, the clinical symptoms were evaluable in 31 embolization procedures. A decrease of clinical complaints was found in 55%. Embolization therapy has been shown to be a safe and effective noninvasive procedure, which in this study is confirmed by the low treatment failure

of only four embolizations, and can be combined with all other treatment options, and complications are not common (11,12).

The second advantage of embolization therapy is that it can be used to prepare selected patients for surgery of the targeted metastatic lesion. This was done in four of our patients. Metastatic thyroid lesions, especially in bones, are hypervascular. By means of preoperative embolization, the intraoperative blood loss can be reduced (10), as has been shown in metastatic renal cell carcinomas (27).

Irradiated metastases can also be embolized to decrease local tumor progression. Five patients in our series had been irradiated before embolization therapy, and this did not make the procedure more difficult.

The present study was not designed to determine the effect of SET on life expectancy because there were important clinical differences between SET and non-SET patients. Based on a comparison of these groups, however, it seems unlikely that SET has an important impact on life expectancy. This is not surprising because, for the most part, SET only targets a portion of the tumor burden. It is also consistent with other reports regarding SET as a treatment for thyroid and other cancers. Wirbel *et al.* (28) reported that preoperative embolization of spinal and pelvic metastases of different primary tumors, mostly renal cell carcinoma, had no influence on survival time. In the study of Bernier *et al.* (29), 34 of 109 (31%) patients with DTC received selective arterial embolization therapy as preoperative and/or palliative treatment for bone metastases. No improvement in survival was noted. In the future, specific systemic treatment modalities for patients with DTC and hematological spread disease might possibly be more effective to improve survival. For improvement of survival, an aggressive multidisciplinary approach has been advocated (30), but local therapies for tumor control, like embolization therapy, are very valuable to the preservation of quality of life.

In conclusion, life expectancy in patients with metastatic disease is not improved by embolization therapy, but a significant effect on complaints and reduction of tumor burden was found. Embolization therapy can be used for tumor debulking, devascularization of tumor before surgery, and pain reduction, and can be combined with other treatment modalities such as radiation.

Disclosure Statement

No competing financial interests exist.

References

1. Links TP, Van Tol KM, Jager PL, Plukker JT, Piers DA, Boezen HM, Dullaart RP, De Vries EG, Sluiter WJ 2005 Life expectancy in differentiated thyroid cancer: a novel approach to survival analysis. *Endocr Relat Cancer* **12**:273–280.
2. Krenning EP, Valkema R, Kooij PP, Breeman WA, Bakker WH, De Herder WW, Van Eijck CH, Kwekkeboom DJ, De Jong M, Jamar F, Pauwels S 2000 The role of radioactive somatostatin and its analogues in the control of tumor growth. *Recent Results Cancer Res* **153**:1–13.
3. Feldman F, Casarella WJ, Dick HM, Hollander BA 1975 Selective intra-arterial embolization of bone tumors. A useful adjunct in the management of selected lesions. *Am J Roentgenol Radium Ther Nucl Med* **123**:130–139.

4. Camille RR, Leger FA, Merland JJ, Saillant G, Savoie JC, Riche MC 1980 Recent advances in the treatment of bone metastases from cancer of the thyroid (author's translation). *Chirurgie* **106**:32–36.
5. Ikejiri K, Furuyama M, Muranaka T, Anai H, Takeo S, Sakai K, Saku M, Yoshida K 1997 Carcinoma of the thyroid manifested as hyperthyroidism caused by functional bone metastasis. *Clin Nucl Med* **22**:227–230.
6. Ramos HE, Braga-Basaria M, Haquin C, Mesa CO, Noronha L, Sandrini R, Carvalho Gde A, Graf H 2004 Preoperative embolization of thyroid arteries in a patient with large multinodular goiter and papillary carcinoma. *Thyroid* **14**: 967–970.
7. Elshafie O, Hussein S, Jeans WD, Woodhouse NJ 2000 Massive rise in thyroglobulin with adult respiratory distress syndrome after embolisation of thyroid cancer metastasis. *Br J Radiol* **73**:547–549.
8. Keller FS, Rösch J, Bird CB 1983 Percutaneous embolization of bony pelvic neoplasms with tissue adhesive. *Radiology* **147**:21–27.
9. Smit JW, Vielvoye GJ, Goslings BM 2000 Embolization for vertebral metastases of follicular thyroid carcinoma. *J Clin Endocrinol Metab* **85**:989–994.
10. Yamasoba T, Kikuchi S, Sugawara M, Higo R, Sasaki T 1994 Occult follicular carcinoma metastasizing to the sinonasal tract. *ORL J Otorhinolaryngol Relat Spec* **56**:239–243.
11. Van Tol KM, Hew JM, Jager PL, Vermey A, Dullaart RP, Links TP 2000 Embolization in combination with radioiodine therapy for bone metastases from differentiated thyroid carcinoma. *Clin Endocrinol (Oxf)* **52**:653–659.
12. Eustatia-Rutten CF, Romijn JA, Guijt MJ, Vielvoye GJ, Van den Berg R, Corssmit EP, Pereira AM, Smit JW 2003 Outcome of palliative embolization of bone metastases in differentiated thyroid carcinoma. *J Clin Endocrinol Metab* **88**:3184–3189.
13. Tazbir J, Dedecjus M, Kaurzel Z, Lewinski A, Brzeziński J 2005 Selective embolization of thyroid arteries (SETA) as a palliative treatment of inoperable anaplastic thyroid carcinoma (ATC). *Neuro Endocrinol Lett* **26**:401–406.
14. Dedecjus M, Tazbir J, Kaurzel Z, Lewinski A, Strozyk G, Brzezinski J 2007 Selective embolization of thyroid arteries as a preresective and palliative treatment of thyroid cancer. *Endocr Relat Cancer* **14**:847–852.
15. Guzman R, Dubach-Schwizer S, Heini P, Lovblad KO, Kalbermatten D, Schroth G, Remonda L 2005 Preoperative transarterial embolization of vertebral metastases. *Eur Spine J* **14**:263–268.
16. Radeleff B, Eiers M, Lopez-Benitez R, Noeldge G, Hallscheidt P, Grenacher L, Libicher M, Zeifang F, Meeder PJ, Kauffmann GW, Richter GM 2006 Transarterial embolization of primary and secondary tumors of the skeletal system. *Eur J Radiol* **58**:68–75.
17. Börüban S, Sancak T, Yildiz Y, Sağlik Y 2007 Embolization of benign and malignant bone and soft tissue tumors of the extremities. *Diagn Interv Radiol* **13**:164–171.
18. Vetter SC, Strecker EP, Ackermann LW, Harms J 1997 Preoperative embolization of cervical spine tumors. *Cardiovasc Intervent Radiol* **20**:343–347.
19. Barton PP, Waneck RE, Karnel JF, Ritschl P, Kramer J, Lechner GL 1996 Embolization of bone metastases. *J Vasc Interv Radiol* **7**:81–88.
20. Smit JW, Van Tol KM, Hew JM, Vielvoye GJ, Romijn JA, Links TP 2001 Marimastat therapy as adjuvant to selective embolization in skeletal metastases of differentiated thyroid carcinoma. *Clin Endocrinol (Oxf)* **55**:421–422.
21. Haveman JW, Phan HT, Links TP, Jager PL, Plukker JT 2005 Implications of mediastinal uptake of ¹³¹I with regard to surgery in patients with differentiated thyroid carcinoma. *Cancer* **103**:59–67.
22. Persoon AC, Van Den Ouweland JM, Wilde J, Kema IP, Wolffenbittel BH, Links TP 2006 Clinical utility of an automated immunochemiluminometric thyroglobulin assay in differentiated thyroid carcinoma. *Clin Chem* **52**:686–691.
23. Zettinig G, Fueger BJ, Passler C, Kaserer K, Pirich C, Dudczak R, Niederle B 2002 Long-term follow-up of patients with bone metastases from differentiated thyroid carcinoma—surgery or conventional therapy? *Clin Endocrinol (Oxf)* **56**:377–382.
24. Gerfo PL, Colacchio T, Colacchio D, Feind C 1978 Serum clearance rates of immunologically reactive thyroglobulin. *Cancer* **42**:164–166.
25. Feldt-Rasmussen U, Petersen PH, Nielsen H, Date J, Madsen CM 1978 Thyroglobulin of varying molecular sizes with different disappearance rates in plasma following subtotal thyroidectomy. *Clin Endocrinol (Oxf)* **9**:205–214.
26. Uller RP, Van Herle AJ, Chopra IJ 1973 Comparison of alterations in circulating thyroglobulin, triiodothyronine and thyroxine in response to exogenous (bovine) and endogenous (human) thyrotropin. *J Clin Endocrinol Metab* **37**:741–745.
27. Manke C, Bretschneider T, Lenhart M, Strotzer M, Neumann C, Gmeinwieser J, Feuerbach S 2001 Spinal metastases from renal cell carcinoma: effect of preoperative particle embolization on intraoperative blood loss. *AJNR Am J Neuroradiol* **22**:997–1003.
28. Wirbel RJ, Roth R, Schulte M, Kramann B, Mutschler W 2005 Preoperative embolization in spinal and pelvic metastases. *J Orthop Sci* **10**:253–257.
29. Bernier MO, Leenhardt L, Hoang C, Aurengo A, Mary JY, Menegaux F, Enkaoua E, Turpin G, Chiras J, Saillant G, Hejblum G 2001 Survival and therapeutic modalities in patients with bone metastases of differentiated thyroid carcinomas. *J Clin Endocrinol Metab* **86**:1568–1573.
30. Haq M, Harmer C 2005 Differentiated thyroid carcinoma with distant metastases at presentation: prognostic factors and outcome. *Clin Endocrinol (Oxf)* **63**:87–93.

Address reprint requests to:

Thera P. Links, M.D., Ph.D.

Department of Endocrinology

University Medical Center Groningen

P.O. Box 30001

9700 RB Groningen

The Netherlands

E-mail: t.p.links@int.umcg.nl