Selective embolization of thyroid arteries as a preresective and palliative treatment of thyroid cancer

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Abstract

Although many tumours of head and neck have been successfully embolized, the number of publications on the application of selective embolization of thyroid arteries (SETA) is limited. The aim of the present study is to evaluate the safety, efficacy and possible indications and contraindications for preresective or palliative SETA in thyroid cancer. The study group comprised 20 patients with thyroid tumours: 7 cases of advanced inoperable anaplastic thyroid cancer (ATC) and 13 cases of differentiated thyroid carcinoma (DTC). All the patients underwent SETA of the superior and/or inferior thyroid arteries. After SETA, selective angiographies of thyroid arteries were performed to ensure that the targeted arteries had been completely occluded. In all the cases, SETA decreased the blood flow through the thyroid. Preresective SETA limited bleeding during surgery and decreased operating time. We observed a massive increase of thyroglobulin (Tg) concentrations in cases of DTC that started 36–48 h after SETA and did not occur in cases of ATC. Although SETA had no influence on the mortality of ATC patients, they reported improvements in swallowing, breathing and decrease of the pain. Concluding, SETA is minimally invasive and safe method limiting blood flow through thyroid tumours. In DTC patients, SETA causes ischaemic necrosis of the gland which results in important increases in serum concentrations of Tg. Therefore, thyroidectomy should be performed during the first 36 h after preresective embolization. Moreover, SETA may become an attractive option of palliative treatment for ATC patients with intractable bleeding, pain or signs of tracheal and oesophageal compression.

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Introduction

Embolization of vascular tumours of the head, neck and central nervous system (CNS) has become an important adjunct to the surgical treatment of these tumours. Introduction of the procedure has resulted in reduced morbidity and mortality of patients with the tumours in question, while it also facilitates their removal. In tumours that are not amenable to surgical therapy, embolization is used as the primary mode of treatment. Palliative embolization of the head, neck and CNS tumours is indicated as the sole treatment for patients who are at poor risk for surgery, radiation therapy or chemotherapy for intractable pain, intractable haemorrhage or increasing neurological deficits (American Society of Interventional and Therapeutic Neuroradiology 2001, Lookstein & Guller 2004).

Despite the good results, obtained in embolizations in the head, neck and CNS tumours, the number of publications, considering the application of selective embolization of thyroid arteries (SETA) in the treatment of thyroid diseases, is limited. In Xiao et al. (2002), their work proposed arterial embolization as a novel approach to thyroid ablative therapy. The authors performed selective arteriography, using Seldinger (1953) technique, followed by embolization of thyroid arteries in 22
patients with Graves’ disease. From that group of the patients, 14 remained euthyroid after SETA, 6 were operated on because of goitres and 2 needed a maintenance dose of anti-thyroid therapy. The investigators did not note any serious complications in any of those patients. After almost 2-year follow-up, they stated this procedure to be effective, minimally invasive and safe. On the other hand, there are some reports on the effective use of SETA in the treatment of vascular lesions of the thyroid arteries (Perona et al. 1999, Jeganath et al. 2001, Kos et al. 2001, Garrett et al. 2005). Also numerous studies have been performed on embolization of the skeletal metastases from the differentiated thyroid cancer (DTCs; Court et al. 2000, Smit et al. 2000, van Tol et al. 2000, Eustatia-Rutten et al. 2003, Lorenz et al. 2005). The number of studies on SETA application in primary thyroid cancer is limited and they are based on small number of patients (Beers et al. 1985, Ramos et al. 2004, Tazbir et al. 2005).

Since the application of SETA may be regarded as an alternative and/or an addition to the existing treatment of selected cases of thyroid cancer in the present study, the usefulness of SETA was evaluated as a pretreatment to thyroid surgery in selected cases of DTC. It was also analysed as a palliative therapy in selected cases of advanced inoperable anaplastic thyroid carcinoma (ATC).

**Patients and methods**

The study group comprised 20 patients: 13 with invasive DTC (Table 1) and 7 with advanced stages of inoperable ATC (Table 2). The patients were enrolled in the study from June 2003 to June 2006. The study protocol had been approved by the Ethics Committee of the Medical University of Lodz. The patients were informed of the procedure, associated risks and potential side effects; afterwards, they signed a consent form as their approval to undergo arterial embolization (Fig. 1).

**SETA**

All the patients underwent SETA of the superior and/or one of the two inferior thyroid arteries. The procedure was performed by a qualified team, using the Seldinger’s technique (Seldinger 1953). A typical procedure required <1 h (from 20 to 90 min). In brief, the patient was placed in a supine position. The inguinal pulsation point of either the left or the right femoral artery was chosen as the puncture site. A small skin incision was made under local anaesthesia (1% procaine, 2–3 ml). The puncture needle, along with a cannula, was inserted into the femoral artery through the incision. Next, the needle was removed, while the cannula remained in the vessel lumen as an entry portal for a 4 or 5 F-size angiographic catheter (Vertebral – Cordis, Europe NV, The Netherlands and Multipurpose, Balton, Poland). The catheter was advanced from the femoral artery via the abdominal aorta and, sequentially, to both the superior and one of the inferior thyroid arteries. Migration of the catheter was visualized through the use of a digital imaging X-ray device (Angiorey DFP-50A, Toshiba, Japan).

<table>
<thead>
<tr>
<th>No.</th>
<th>TNM</th>
<th>Staging</th>
<th>Tumour diameter (cm/l)</th>
<th>Thyroid volume (ml)</th>
<th>Time between SETA and CT scan (h)</th>
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<tbody>
<tr>
<td>1</td>
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<td>III</td>
<td>7.75</td>
<td>280.5</td>
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<td>5.45</td>
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<td>5.35</td>
<td>158</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>T₃N₀M₀</td>
<td>III</td>
<td>4.65</td>
<td>148</td>
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</tr>
<tr>
<td>6</td>
<td>T₃N₁M₀</td>
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<td>6.20</td>
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</tr>
<tr>
<td>7</td>
<td>T₃N₁M₁</td>
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<td>4.30</td>
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<tr>
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<td>216</td>
<td></td>
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<tr>
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<td>4.50</td>
<td>172</td>
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<tr>
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<tr>
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<td>III</td>
<td>5.20</td>
<td>210</td>
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</table>
Before embolization, a contrast media (Ultravist 300; Schering AG, Germany) was injected into the vessels, thus allowing us to visualize the arteries and regions of the thyroid to which they supplied blood. Granules consisting of polyvinyl alcohol (PVA, Cordis Neurovascular Inc., Miami, FL USA), ranging from 150 to 750 μm, were slowly injected into the vessels. An added step for embolizing the superior arteries involved the use of a non-magnetic wire coil with synthetic fibres (MReye IMWCE 35-5-8, Cook, Denmark) of appropriate size, depending on the diameter of the lumen of the arteries in question. After SETA, selective angiography of the thyroid arteries – as digital subtraction angiography (DSA) images – was performed to ensure complete occlusion of the targeted arteries.

### Determination of concentrations of free triiodothyronine (FT₃), thyroxine (FT₄), thyrotropin (TSH), thyroglobulin (Tg), parathormone (PTH) and calcium (Ca⁺⁺)

The Tg, FT₃, FT₄, TSH and PTH concentrations were measured using electrochemiluminescence method with a Modular E170 (Roche) analyser and appropriate kits (Roche-Diagnostics).

### Imaging diagnostics

All the patients were diagnosed by ultrasound examination ultrasound Doppler imaging and fine needle aspiration biopsy. The examinations were performed before SETA as a routine procedure, and after SETA, in order to estimate its effect on thyroid vascularization and morphology. Before SETA, angio-16 W CT scan with 3D reconstruction was performed in all the cases. The patients with important stenosis (>70%) of internal carotid arteries were disqualified from SETA, except for ATC patients with bleeding from the tumour. In order to estimate the effectiveness of SETA and changes in the thyroid after embolization in selected cases, angio-16 W CT scan with 3D reconstruction was performed 1–6 days after SETA. All the patients had thyroid angiography just before SETA (to estimate the vascularization status of the organ and choose the right diameter of PVA granules) and immediately after embolization (to estimate the effect of SETA and ensure the closure of targeted arteries).

### Statistical analyses

Paired t-test was used to evaluate differences in the concentrations of biochemical parameters (with

### Table 2 Clinical characteristics of the seven patients with anaplastic thyroid cancer (ATC) who underwent palliative selective embolization of thyroid arteries (SETA)

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Breathing</th>
<th>Swallowing</th>
<th>Pain relief</th>
<th>Haemostatic effect</th>
<th>General condition</th>
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<td>45</td>
<td>M</td>
<td>0</td>
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<tr>
<td>2</td>
<td>78</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>0</td>
<td>N/A</td>
<td>0</td>
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<tr>
<td>3</td>
<td>72</td>
<td>F</td>
<td>+</td>
<td>0</td>
<td>+</td>
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<td>+</td>
</tr>
<tr>
<td>4</td>
<td>80</td>
<td>F</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>N/A</td>
<td>+</td>
</tr>
<tr>
<td>5</td>
<td>81</td>
<td>F</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>N/A</td>
<td>+</td>
</tr>
<tr>
<td>6</td>
<td>68</td>
<td>F</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>+</td>
<td>+</td>
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<tr>
<td>7</td>
<td>85</td>
<td>F</td>
<td>+</td>
<td>0</td>
<td>+</td>
<td>NA</td>
<td>0</td>
</tr>
</tbody>
</table>

M, male; F, female; +, improvement; 0, no effect; −, aggravation; N/A, not applicable.
normal distribution) in patients before and after SETA. For comparison of Tg concentration, the non-parametric Mann–Whitney U test was used. Unpaired t-test was used to assess whether there was any difference in operating time and blood loss between the patients, thyroidectomized because of DTC after preoperative embolization and thyroid volume-matched patients, and thyroidectomized because of DTC without preoperative embolization. Coefficients of correlation, r and P, were calculated using linear regression analysis and Spearman’s rank correlation analysis as appropriate. The level of statistical significance was set at P<0.05. Unless otherwise stated, the values are expressed as the means ± s.d.

Results

SETA in DTCs

In all the patients, SETA effectively limited blood flow through the thyroid arteries confirmed immediately after embolization by angiography and, later, by CT scan and/or ultrasound examination. We did not observe any changes in thyroid volume, either before or after embolization (90.4 ± 26.4 ml versus 88.9 ± 24.9 ml). We noted a massive increase in serum Tg concentration after SETA (130.9 ± 48.89 vs 15 441.26 ± 41 895.9 respectively; P<0.003, Table 3), which was related to the time period between embolization and thyroidectomy (r=0.69, P<0.001). Together with Tg increase, we observed an increase of free thyroid hormone concentrations (FT4 15.01 ± 3.1 vs 20.15 ± 4.55 respectively, P=0.052 and FT3 4.79 ± 0.88 vs 6.1 ± 8.5 respectively, P<0.008) and a consequent decrease of TSH concentrations (2.96 ± 1.3 vs 1.6 ± 1.47 respectively, P<0.006, Table 3). In all the patients, calcium and PTH concentrations were within the normal range before and after embolization, although slight fluctuations were observed (Table 3).

No major complications were observed, although we noted haematoma (five cases), fever (six cases) and neck pain (five cases). Comparing thyroidectomies, performed after SETA to 20 thyroidectomies performed because of DTC without preoperative therapy (selected patients had similar thyroid volume), we noted a significant decrease of the operating time (123 ± 24 min versus 95.8 ± 26 min respectively, P<0.01), intraoperative blood loss (138.2 ± 29.2 g versus 49.9 ± 12.7 g respectively, P<0.0001) and drainage in the first 24 h (160 ± 25 ml versus 92 ± 9 ml respectively, P<0.0001).
SETA in anaplastic thyroid cancer

Palliative SETA in cases of inoperable ATC effectively limited blood flow through the gland. The patients reported improvement in breathing (six patients), swallowing (two patients) and pain decrease (four patients). In two patients after SETA, stridor disappeared and, in other two cases, SETA stopped bleeding from the tumour. Five patients reported improvement of the general condition (Table 2).

Discussion

The indicators of embolization efficacy include technical and clinical success. The technical success of embolization is defined as occlusion of the targeted vessels. We achieved the technical success in all the patients, which was confirmed in angiography and angio-CT scans. However, in order to avoid hypoparathyroidism, we embolized only one out of the two inferior thyroid arteries. The parathyroid glands usually derive most of their blood supply from the inferior thyroid artery, although branches from the superior thyroid artery supply at least 20% of upper glands (Lal & Clark 2005). This is the reason for why in thyroid surgery ligation of the main trunk of the inferior thyroid artery is not a standard procedure, and also for why we decided not to perform embolization of both inferior thyroid arteries. Vascularization of other important adjacent structures (the oesophagus, trachea and recurrent laryngeal nerves) does not depend on thyroid arteries in important manner, so their blood supply is not likely to be affected by SETA.

The clinical success of embolization is defined as a decrease in the expected blood loss during surgery and/or facilitated tumour removal, and/or reduced surgical complication and/or palliation of the symptoms associated with tumour presence (The American Society of Interventional and Therapeutic Neuroradiology 2001, Lookstein & Guller 2004). The potential advantages of performing SETA before thyroidectomy include shortening of the operative procedure time and increasing the chances of complete surgical resection. Moreover, SETA should allow better visualization of the surgical field with decreased overall surgical complication rate as an effect of limited intraoperative bleeding. The latter point would be of particular importance in thyroid cancer surgery because of the relatively high risk of the damage of surrounding tissue, including parathyroid glands, recurrent laryngeal nerve and oesophagus. While comparing thyroidectomies in advanced DTC, performed after SETA and without preresective embolization, we did not observe any statistical differences, regarding either transient postoperative complications or postoperative definitive sequels. It should be noted that the analysed groups were not randomized and SETA was performed in the cases with the worst prognosis. In the patients with preresective SETA, we observed evident and statistically significant decrease of the operating time and reduced blood loss. Although the operating time and blood loss are of extreme importance, especially in patients with advanced cancer, the differences are, in our opinion, too small to justify routine application of preresective SETA in patients with advanced DTC. However, in favour of preresective SETA, the operating surgeons have reported that preresective embolization facilitated tumour removal. No major or even minor bleeding allowed performing radical manoeuvres which accelerated operation. In some studies, the authors reported reduction of the gland volume after SETA (Xiao et al. 2002, Ramos et al. 2004, Zhao et al. 2007). We compared CT scans of the tumour for 1, 2, 4 and 6 days before and after embolization. There was no difference in thyroid volume, probably, because of the short period between SETA and thyroidectomy. However, we noted structural changes in the gland, which may have been responsible for differences in its consistency, facilitating tumour removal.

Massive increase of Tg concentration and moderate increase of free thyroid hormones are, in our opinion, the effects of ischaemic necrosis of the thyroid gland. Although, SETA limits thyroid blood supply, the veins are not closed and the blood outflow is not limited. In consequence, colloid from dying thyrocytes (comprising Tg, T3, T4 and, probably, other biochemical compounds) gets into circulation. The review of literature did not help us to elucidate potential consequences of increased serum Tg concentration. However, in the earlier study, the authors described that embolization of DTC metastases caused massive Tg increase, which, probably, resulted in adult respiratory distress syndrome (Elshafie et al. 2000). Considering the above, we suggest performing thyroidectomy up to the 36 h after preresective SETA, as till that time we did not observe any important increase in the concentration of the parameters in question.

In the investigated group, SETA effectively palliated the symptoms related to tumour presence in ATC patients. The patients reported improvement of breathing, swallowing, a decrease of the pain of the neck and improvement of the general condition. However, most of these symptoms are subjective and psychological effect of the therapy cannot be excluded.
The most spectacular effects of SETA included the anti-haemorrhage effect of embolization in case of intractable bleeding from ATC and the disappearance of stridor after tumour embolization. Since the main goal of the palliative therapy is the improved quality of patient’s life, we believe that SETA, as an effective, minimally invasive and safe method, may become a valuable addition to the therapeutic strategies for inoperable ATC. However, in our opinion, this kind of treatment can only find application in selected cases of advanced thyroid cancer. On the other hand, selective catheterization of thyroid arteries, together with SETA, may potentially become a valuable tool for local chemotherapy, local gene therapy or local immunological therapy of advanced thyroid cancer (Table 3).

Acknowledgements
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References