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Original article

TRANSCATHETER ARTERIAL EMBOLIZATION OF HYPERVASCULAR BONE METASTASES IN REDUCING PERIOPERATIVE BLEEDING AND PAIN

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ABSTRACT

Evaluate the effect of TAE in reducing intraoperative bleeding and algic symptoms in hypervascular bone metastases. Between January 2016 and May 2021, 101 embolizing procedures were performed in 83 patients with hypervascular bone metastases. The primary tumors were renal cell cancer, thyroid cancer and adrenal cancer. Indications were preintervention in 30 cases and palliative treatment in 53 cases; 18 patients treated with palliative TAE had a local recurrence of disease so we indicated a second palliative TAE. A grade 1 devascularization was obtained in 91 targeted lesions. In patients candidates for surgical exeresis, the intervention was performed within 48-72 hours after TAE and no cases of major intraoperative bleeding were reported. All patients who were not operated on, after TAE presented a significative pain relief. Between pain relief and devascularization grade we found a very strong correlation (r = 0.96). TAE reduces perioperative bleeding risk and improves algic symptoms as palliative treatment.

1. Introduction

Metastatic bone tumors are a major cause of morbidity and mortality in the context of tumor pathology [1]. Bone metastases can be asymptomatic, although in more than 80% of cases they result in pain and half of patients suffer from skeletal complications such as pathological fractures, spinal cord compression and hypercalcemia [2].
These complications, in addition to the important pain, could cause a deterioration in the patients' life quality and also lead to a reduction in overall survival [3], conditioning also a decreased mobility and a loss of patient autonomy [4]. Bone metastases mainly derive from breast, lung, renal, thyroid and prostate cancer, occurring in about 70% of cases; bone metastases are less frequent in gastrointestinal tumors in which they affect only 20% of patients [5]. The most frequent sites of bone metastases are skull, ribs, spine, pelvic bones and the proximal ends of long bones [6].

Treatments for bone metastases include surgery, chemotherapy, radiation therapy, minimally invasive percutaneous thermoablative treatments, cementoplasty, intraarterial embolization and mixed treatments.
The choice of the treatment depends on localization, number and size of bone metastases, condition of the patient and stage of disease.
First, patients are referred to analgesics, then to radiotherapy and to other treatments [7].
However, treatments efficacy is often poor in patients with bone metastases that presents important painful symptoms refractory to common therapy [8], requiring massive narcotic use with significant side effects [9].
Transcatheter arterial embolization (TAE) of metastatic bone tumors has a wide range of indications, from curative treatment to palliation. TAE is indicated in the treatment of hypervascular bone metastases.
TAE can be used to reduce pain also in association with other treatments

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[10], to reduce bleeding during surgery [11-12] or also as cytoreductive palliative treatment for the local control of the disease [13]. Without TAE, surgical treatment of hypervascular bone metastasis is burdened by a high hemorrhagic risk [14,15].

The purpose of this study was to evaluate the effect of TAE in patients with hypervascular bone metastases in reducing surgical intraoperative bleeding and in assessing the clinical response in palliation in patients not treated surgically.

2. Material Methods

Between January 2016 and May 2021, we retrospectively selected 83 patients (51 men and 32 women) with an average age of 64.8 years (range from 37 to 84 years), that underwent to selective TAE of hypervascular bone metastases; 18 patients treated with palliative TAE had a local recurrence of disease and underwent to a second selective TAE, with the overall execution of 101 embolizing procedures. The primary tumors were renal cell cancer, thyroid cancer and adrenal cancer respectively in 53 (63.8%), 25 (30.1%) and 5 (6.1%) patients. Bone secondary lesions involved lumbar spine in 8 patients, pelvis in 40, femur in 10, humerus in 18 and shoulder girdle in 7 patients.

Every lesion treated showed hypervascularity in a preprocedural contrast-enhanced CT examination (Figure 1) and was candidated for TAE. The indications of TAE were preintervention in 30 cases and palliative treatment in 53 cases with important pain; 18 patients treated with palliative TAE had a local recurrence of disease so we indicated a second palliative treatment with TAE.

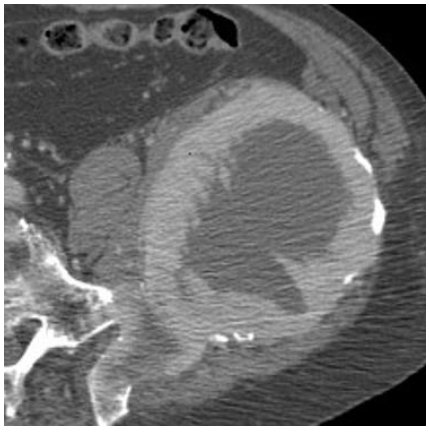

Figure 1. A 68-year-old man with severe pain in left iliac fossa due to iliac metastasis from thyroid cancer. CT image shows a wide osteolytic lesion with important hypervascular peripheral component.

Before TAE, all patients underwent blood chemistry tests to verify that there was no severe alteration of the coagulation status (INR major than 2.0) or severe thrombocytopenia (number of platelets minor than 50,000 units per mm^3).

The interventional procedures were performed from a common femoral approach previa local anesthesia. A pre-procedural diagnostic angiogram was performed in order to evaluate the regional arterial anatomy, identify the tributary vessels of the neoplasm and exclude the presence of shunts with adjacent critical arterial districts.

A 5-Fr catheter was used in conjunction with a coaxially placed 2,0- to 2,7-Fr microcatheter to selectively catheterize target arteries supplying bone metastases (Progreat Micro Catheter System, Terumo Interventional Systems; Direxion Torqueable Microcatheter, Boston Scientific) (Figure 2).

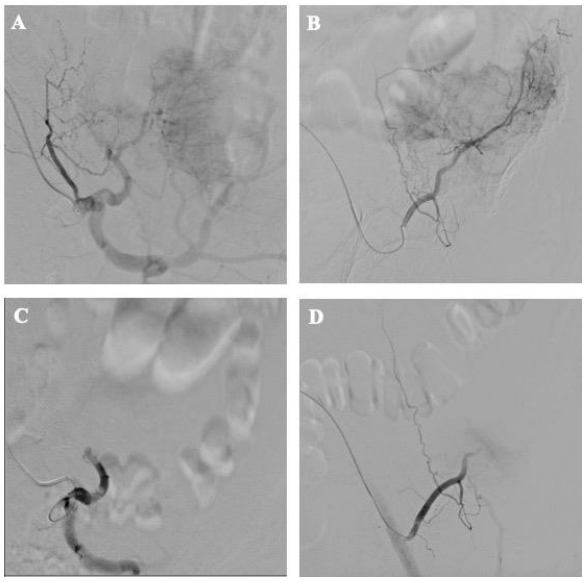

Figure 2. A-B The selective arteriography of some branches of left external iliac artery of the same patient of Fig. 1 revealed the hypervascular neoplastic tissue. C-D Post-procedural arteriography revealed the complete devascularization of the lesion.

As embolic agents we used microspheres of 300-500, 500-700 and 700-900 micron (Embosphere microspheres, Merit Medical Systems; EmboGold microspheres, Merit Medical Systems).

We often used particles of different sizes in association with each other to reach to obtain a better result in embolization (Table 1).

Evaluate items in this study were: technical success, complications, intraoperative bleeding and clinical response.

Technical success was evaluated with completion angiography and each lesion was categorized on the basis of devascularization grade [16].

Grade 1 was >75% reduction of tumor blush; grade 2, 50-75% reduction of tumor blush; grade 3, <50% reduction of tumor blush.

Complications were categorized in according to Society of Interventional Radiology [17].

Major complications result in admission to a hospital for therapy, an unplanned increase in the level of care, prolonged hospitalization, permanent adverse sequelae or death. Minor complications result in no sequelae; they require nominal therapy or a short hospital stay.

Intraoperative blood loss was evaluated in number of packed red blood cell on the basis of postoperative hemoglobinemia values and the difference with preoperative hemoglobinemia values.

The degree of pain was assessed by the subjective reports with a pain rating scale from 0 to 10. A clinical response was defined as a reduction of pain greater or equal to 50% than algic symptoms before TAE; an absence of response was defined as a reduction of pain less than 50% or unchanged pain or progressive pain.

Microspheres	TAE procedures
300-500 µm only	11
300-500 and 500-700 µm	63
500-700 and 700-900 µm	27

Table 1. Size of microspheres in our TAE procedures.

Statistical Analysis

Differences in the pain rating scale of preprocedure and postprocedure were analyzed by two-sided Wilcoxon's signed-rank test. Differences with $P < 0.05$ were considered significant. Spearman's rank correlation test was used to assess correlation between the devascularization grade and the pain relief and classified as follows:

- r 0.70 or higher = very strong positive relationship;
- r from 0.40 to 0.69 = strong positive relationship;
- r from 0.30 to 0.39 = moderate positive relationship;
- r from 0.20 to 0.29 = weak positive relationship;
- r < 0.20 = no or negligible relationship.

3. Results

Diagnostic angiograms confirmed hypervascularizations of all targeted lesions.

A grade 1 devascularization was obtained angiographically in n. 91 procedures (Figure 3-4); grade 2 devascularization was reached in n. 10 cases. Grade 3 devascularization was obtained in no one lesion.

In patients candidates for surgical exeresis of the lesion, the intervention was performed within 48-72 hours after TAE and no cases of major intraoperative bleeding were reported. It was necessary to recur to transfusion of 2 packed red blood cell in only 1 case that presented hemoglobinemia <7 gr/dl. In all other cases postoperative hemoglobinemia was >8 gr/dl and it was not necessary to transfuse packed red blood cell (mean preoperative Hb values 11.5 gr/dL, mean postoperative Hb values 9 gr/dL).

All patients who were not operated on, after the embolization procedure presented a clinical response (reduction of pain more than 50% respect initial rate) with achievement of the maximum response within 48 hours after the procedure, with a significant reduction of grade of pain in relation to the grade of devascularization ($P<0.01$).

No significative difference in terms of technical success was found between lesions treated with different size of microparticles.

The duration of the analgesic effect attested around 8 months (range from 2 to 13 months).

No major periprocedural complications were observed. As minor complications we observed local pain in 11 patients that completely solved in 2 days.

During the follow-up period 18 patients treated with palliative TAE suffered a relapse of algic symptoms at an average of 6 months (range from 2 to 12 months) for local recurrence of disease and they underwent to a second TAE procedure.

Between pain relief and devascularization grade we found a very strong correlation (r = 0.96) (Table 2).

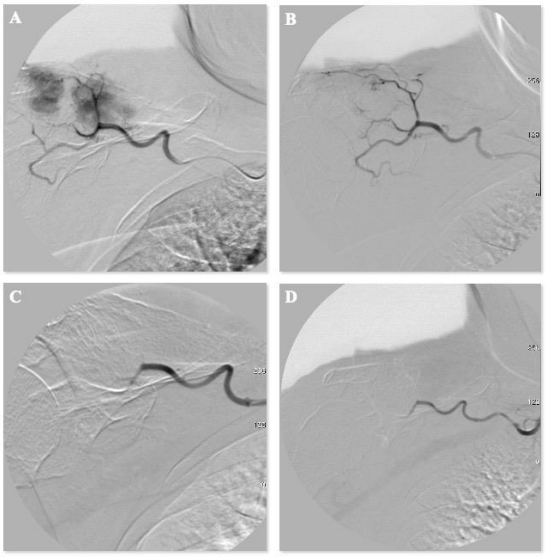

Figure 3. 76-year-old woman with renal cancer and with a single hypervascular bone lesion in the right clavicle. The patients complained of severe pain unresponsive to analgesic therapy. A Selective diagnostic angiography from the suprascapular artery revealed neoplastic hypervascularity in the lateral third of the clavicle involving adjacent soft tissues. B-D TAE with EmboGold microspheres of 300-500 µm and 500-700 µm allowed complete devascularization of tumoral tissue and the technical success of the procedure.

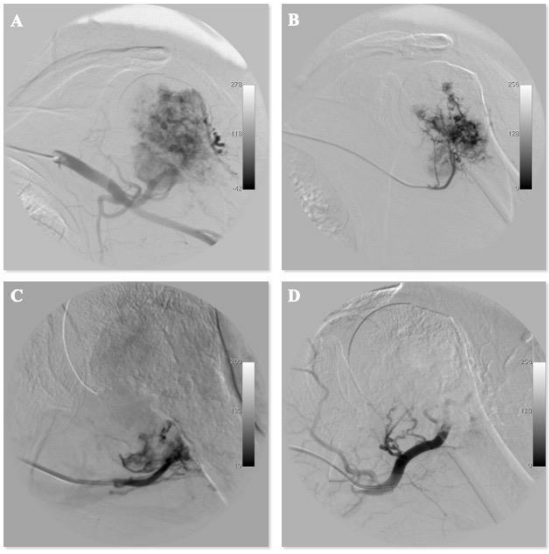

Figure 4. A Diagnostic angiography from axillary artery and B selectively from posterior circumflex humeral artery revealed hypervascular neoplastic tissue. C-D TAE with EmboGold microspheres of 300-500 µm, 500-700 µm and 700-900 µm determined complete devascularization of the hypervascular tissue.

Grade of devascularization	Mean pain value before TAE [a]	Mean pain value after TAE [a]
1	9	0
2	9	3

[a] In a rating scale from 0 to 10

Table 2. Mean pain values before and after palliative TAE in patients that didn't underwent to surgery (no. 71 procedures in 53 patients).

4. Discussion

In literature there was not a universal agreement in use of TAE for treatment of hypervascular bone metastases. TAE is useful for palliative treatment of metastatic hypervascular tumor, also in association with surgery [18].

All patients with hypervascular bone metastases, especially from renal cell cancer and thyroid cancer, should be considered as candidates for such a procedure which can be technically successfully completed in the majority of cases [19], but at current state TAE rarely is considered treatment of choice for bone metastases.

In the treatment of metastasis from hypervascular tumors TAE is effective in reduction of risk of perioperative bleeding reducing estimated blood loss and packed red blood cell transfusion volume [20]. Instead TAE is not very effective in the treatment of metastases from primary hypovascular tumors, such as breast and lung cancer [21]. Whenever possible, it is recommended to perform surgery within 48 hours after the embolization procedure to obtain the best result in terms of control of intraoperative bleeding [22]. In our study we reported a very low bleeding rate in terms of postoperative hemoglobinemia and red blood cell transfusion volume with only 1 patient with hemoglobinemia < 7 gr/dl that needed 2 packs of red blood cells. In all other cases we didn't need to transfuse packed red blood cells.

Palliative TAE is also useful in pain relief in patients with hypervascular bone metastases. Period of pain relief varies from 1 to 9 months, at the end of which, if necessary, it is possible to repeat the TAE which has proven to be a safe procedure [23]. In our work we reported a clinical response in pain relief in all patients that did not underwent to surgery. As suggested by Chuang et al., pain relief could be explained by a reduction of the distension and disruption of richly innerved periosteum by the tumor growth that is slow down by its blood supply from TAE [12]. In addition it could be caused by decreased blood flow and reduction of edema which may determine direct pressure effects on adjacent structures and nerves in the surrounding tissues [16].

Although a complete devascularization of hypervascular metastases is important for clinical response and to help surgeons in intervention, scrupulous technique is required to avoid complications due to embolization of nontarget regions. In particular in case of vertebral metastases, extreme attention must be paid to finding the Adamkiewicz artery which originates in 75% of cases to the left of the aorta between the 8th thoracic and the 1st lumbar vertebra [24] to avoid embolization of the spinal cord with important neurologic sequelae.

Other post-procedural complication of TAE include dermal or muscle necrosis, abscess and post-embolization syndrome with fever, chills, nausea, vomiting, pain and paraesthesia [25].

A severe alteration in the patient's coagulation status or severe thrombocytopenia may contraindicate the embolization procedure if not adequately corrected in advance as some embolizing agents trigger the coagulation cascade and Kasabach-Merritt syndrome may occur [26].

Thus, embolization technique requires scrupulous attention to avoid embolization for nontarget regions. To reach this goal the use of microcatheters for superselective catheterization of arterial vessels afferent to the neoplasm is mandatory as they allow a marked reduction in the risk of embolization of adjacent vascular territories and allow to embolize even small caliber vessels [27].

Tributary arteries must be superselectively catheterized in order to avoid the possible embolization of other arterial districts, which could lead moreover to an increase in the risk of intraoperative bleeding due to reperfusion syndrome [28].

In our work, however, we found a very low rate of complications and those did occur were categorized as minor complications. TAE is repeatable when necessary as we did in 18 patients that had a local recurrence of disease.

Embolic agents currently available are multiple and currently include gelfoam, polyvinyl alcohol (PVA) particles, microspheres, liquid agents, coils, tissue adhesives, and collagen microfibrils [29].

There are several factors that determine the best choice of embolizing material such as the speed of action, the duration of occlusive effect and the protection of healthy tissue. Coils are ideal for single and large-caliber vessels; microspheres are useful in case of multiple small arterial afferents to the neoplastic lesion, with numerous collateral circulation [30]. There are various sizes of coils, microcoils and microspheres, so it is important to choose the correct caliber according to the diameter of any intratumoral shunts and collateral vessels [31]. We used microspheres of 300-500, 500-700 and 700-900 micron. We preferred not to use liquid embolic agents because they can cause a more extensive tumor necrosis, generating an increased ischemic pain at the embolization site after the procedure [32].

There are some limits to this work. First, we did not carry out a survival analysis of the patients treated. Several works underline that life expectancy is not improved by embolization of bone metastases [33], but it is still predictable as embolization has a mainly palliative purpose. Second, it was a retrospective study with a small number of patients at a single institute.

Selective TAE of hypervascular bone metastases is a safe and repeatable procedure. TAE reduces perioperative bleeding risk and improve algic symptoms in patients that could not be operated. It can also be associated to other treatment options such as surgery, to reach a more complete pain control.

It's necessary further studies to define a standard protocol of TAE use in treatment of hypervascular bone metastases.

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