The role of transanterial embolization of the renal cell carcinomas (RCC) in elderly and unfit for surgical treatment patients.

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Περίληψη

Ο σκοπός αυτής της μελέτης είναι να παρουσιάσει το ρόλο του χημειοεμβολισμού των νεφρικών καρκινωμάτων και να αξιολογήσει την αποτελεσματικότητά του ως ανακουφιστική θεραπεία των ανεγχείρητων ή/και χαμηλού σταδίου νεφροκυτταρικών καρκινωμάτων ασθενών ακατάλληλων για χειρουργείο. Η ομάδα μελέτης αποτελείτο από 8 διαδοχικούς ασθενείς (3 άνδρες και 5 γυναίκες, με εύρος ηλικίας 71-87 ετών), οι οποίοι υποβλήθηκαν σε παρηγορητικό εμβολισμό νεφρικών καρκινωμάτων μεταξύ Ιανουαρίου 2008 και Δεκεμβρίου 2013. Στις 7 από τις 8 περιπτώσεις ο όγκος ήταν πρωτοπαθής ενώ στην μία ήταν δευτεροπαθής προέλευσης. Σε 1 περίπτωση διαγνώστηκε αμφοτερόπλευρη νόσος. Σε 2 περιπτώσεις υπήρχαν περισσότεροι από ένας όγκος στον πάσχοντα νεφρό. Σε 5 ασθενείς η νόσος ήταν ανεγχείρητη (3 σταδίου IVα και δύο σταδίου IVβ) και σε 3 ήταν δυνητικά χειρουργήσιμη (2 σταδίου II, και ένας σταδίου IIIα). Ωστόσο, οι τελευταίοι 3 ασθενείς αυτοί ήταν ακατάλληλοι για χειρουργική επέμβαση λόγω σοβαρών συνυπαρχόντων προβλημάτων υγείας. Από όλους τους ασθενείς οι 3 παρουσιάστηκαν κυρίως με αιματουρία και οι υπόλοιποι ασθενείς με πόνο στην πλάγια κοιλιακή χώρα ενώ σε μία ασθενή συνυπήρχαν και τα δύο. Ο εμβολισμός των νεφρικών καρκινωμάτων διεξήχθη χρησιμοποιώντας σφαιρίδες και σπιράλ. Κατά το χρόνο της ανάλυσης, 4 ασθενείς έχουν πεθάνει και 4 ασθενείς είναι ακόμα ζωντανοί, με συνολική μέση επιβίωση 17,57 μήνες. Σε 3 από αυτούς οι ασθενείς με μακροσκοπική αιματουρία έγινε μετάγγιση μέχρι τη σταθεροποίηση του επιπέδου της αιμοσφαιρίνης πριν τον εμβολισμό. Επανεμφάνιση της αιματουρίας παρατηρήθηκε σε 2 από αυτούς τους ασθενείς. Στους 5 ασθενείς που παρουσιάστηκαν με πόνο, τα συμπτώματα βελτώθηκαν σε δύο και υποχώρησαν 1σε 3. Η μέση διάρκεια παραμονής στο νοσοκομείο για όλους τους ασθενείς ήταν 5,25 ημέρες.
Abstract

The purpose of this study is to demonstrate the role of transarterial embolization of the renal cell carcinomas and to evaluate its effectiveness as a palliative treatment of patients with unresectable renal cell carcinoma and patients with low stage renal cell carcinoma who are unsuitable for surgery. The study group consisted of eight patients (3 males and 5 females between 71 and 87 years of age), who underwent palliative embolization of renal carcinomas between January 2008 and December 2013. Unresectable disease was present in 4 patients (3 stage Iva and 1 stage IVb). Potentially resectable disease was present in 3 patients (2 stage II and 1 stage IIIa), who were unsuitable for surgical treatment due to serious comorbidities. Metastatic tumor was present in 1 patient. Only 3 were presented with haematuria and the others presented with pain in the lateral abdomen. Embolization of renal tumors was performed using beads and coils. In 3 patients with macroscopic haematuria we performed transfusion to stabilize the hemoglobin level before embolization. In patients who presented with pain, symptoms improved in 2 and disappeared in 3. The average length of hospital stay for all patients was 5.25 days. In conclusion, the embolization of renal tumors is a safe and tolerated solution for the management of patients with unresectable disease, to relieve local symptoms and to improve clinical status with low morbidity and short hospitalization.

Keywords:
renal-cell carcinoma, transarterial embolization

Introduction

Transarterial embolization of the renal cell carcinomas (RCC) was first introduced in the clinical practice in the 1970s as an invasive procedure secondary to arteriography, the latter being the basic diagnostic method for renal tumors identification of the time\(^1\). In general, embolization is widely applied in the treatment of persistent haemorrhage, vascular lesions and tumors. In urology, it has been established in the management of iatrogenic complications-induced haemorrhage following various procedures\(^2\). Embolization aims to block the blood supply in an organ or a certain region and is performed via the introduction
of an angiographic catheter in a blood vessel and the subsequent use of obstruction materials. The materials used for RCC embolization include coils (spirals), beads, cyanoacrylate glues and alcohol solutions. Blood flow blockade causes acute tissue necrosis which in turn results in acute phase response (APR). During its 40 years of use, RCC embolization has been applied as a neoadjuvant or palliative therapy in large or inoperable tumors as well as in the management of persistent haemorrhage and/or pain. Although it mainly contributes in treating symptoms, there are indications that it may offer long-term survival. Indeed, certain studies concluded that RCC embolization may deliver stabilization and/or remission of distant metastases. The exact mechanism explaining the above phenomenon is not known but it could be attributed to an immunoregulational process. In such a case, embolization-induced tumor necrosis (TN) stimulates the immune system of the host as a response to tumor contracture.

**Materials & Methods**

Eight consecutive patients (3 males and 5 females, aged 71-87), were subjected to palliative RCC embolization between January 2008 and December 2013. Unresectable tumors were present in 4 patients (3 stage IVa, 1 stage IVb). Potentially resectable tumors were present in 3 patients (2 stage II, 1 stage IIIa). One patient has metastatic disease induced by rectal adenocarcinoma. In this case the renal tumor measured 7.1 cm and it was located in the upper pole of the right kidney. Four out of the 8 patients of the study were unfit for surgical treatment since they suffered of serious cardiac and pulmonary conditions while one patient was unfit for surgical treatment due to metastatic disease. Haematuria was the main symptom in 3 patients, pain was the main symptom in 4 patients and in one female patient both symptoms co-existed.

The same procedure was followed for all patients who were included in the study: initially, infusion of local anaesthetic (xylocaine 1%) to the side of the catheter insertion was performed followed by catheterization of the femoral artery under radiologic guidance. The angiographic catheter was then advanced up the ventral aorta (Seldinger procedure). Next, a selective catheterization of the renal arteries via a 5-Fr Cobra I hydrophilic catheter, assisted by infused contrast agent was done. Renography completed the first stage of the procedure. Afterwards, highly-selective catheterization of the nutrient arteries of the tumor was performed followed by embolization with intra-arterial infusion of irinotecan loaded microparticles (IAIRIM) (DC-Beads, Biocompatibles diam. 300-500 μm, dosage: 50mg/ml microspheres) as well as with chemo-free microspheres (Embozene, Celonova, diam. 400 μm), complemented by the placement of a spiral, until the almost complete elimination of neovascularization. In case of multiple tumor vascularization, the same procedure is performed separately for each nutrient vessel. Absence of blood flow in the embolized area during angiography was determined as the standard for successful embolization. The favourable outcome was confirmed by standard angiography or CT-scan or ultrasound study with contrast medium (SonoVue, Bracco).
The whole procedure lasted 30 to 60 minutes. In two cases the procedure was repeated. None of the patients presented serious complications other than post-embolization syndrome (PES): In four of the 8 patients temporary creatinine increase (up to 2.8 mg/dl) was occurred. All these patients were monitored after the procedure receiving hydration and IV antibiotics until the syndrome remitted and the renal function was restored. At the time of analysis, 4 patients were deceased and 4 patients are still alive. The median overall survival (OS) was 15.75 months. In 3 patients with macroscopic haematuria, we performed transfusion to stabilize the pre-embolization haemoglobin levels. Haematuria recurrence was identified in 2 of these patients. Out of the 5 patients presenting with pain, the symptoms improved in 2 and completely resolved in 3. Mean hospitalization for all study patients was 5.25 days.

While the value of RCC embolization in managing related symptoms like pain and haematuria is widely accepted, it is not established whether there is a true survival benefit. Provenza et al\textsuperscript{5}, investigated the efficacy of RCC embolization in a small number of patients with stage III and stage IV RCCs. In total, mean survival was 8.5 months, whereas mean survival for stage III and stage IV RCC patients was 23 and 7 months, respectively. Onishi et al, compared two study groups with unresected disease (stage IV): 24 patients were subjected to embolization and 30 patients did not receive any treatment. Mean survival for the treatment group was 229 days and for the control group 116 days. The subjects who underwent treatment (embolization) manifested a significantly better outcome than those
who were not managed\textsuperscript{6}. Other authors report that the mean survival for all patients subjected to embolization ranges between 4 and 8.4 months. This corresponds to a survival rate of 36.8 and 15.8\% for 1 and 2 years, respectively\textsuperscript{7}. In contradiction, Ridley et al support that embolization does not constitute a therapeutic approach and potentially it does not alter the natural progression of the disease to a great extent, but it palliates the symptoms related to advanced stage diseases\textsuperscript{8}. The fact that RCC embolization could trigger a tumor necrosis-induced immunoregulation response is an intriguing perspective and in fact, in an experimental study, Nakano et al proved that the lymphocytes in RCC patients were embolization-stimulated in vitro\textsuperscript{9}. Nonetheless, RCC embolization has not yet gained wide acceptance, possibly due to the lack of prospective randomized studies proving these presumable benefits. Effective embolization results in tissue or organ ischemic necrosis, which however generates a group of symptoms named post-embolization syndrome (PES) commonly developing within the first post-embolization days\textsuperscript{10}. Patients with smaller or peripheral tumors and patients with long-term sizeable non-embolized normal parenchyma exhibit a greater risk of developing PES\textsuperscript{10}. The syndrome includes: pain in the lumbar area, nausea and vomits, fever and arterial pressure fluctuations\textsuperscript{7}. The symptoms are usually transient and their severity depends on the extension of ischemia in the kidneys region. In a
small percentage, embolization may result in serious complications mainly related to embolization material migration to another organ like the contralateral artery, the mesenterial arteries, the lower limbs arteries and spinal cord ischemic lesion\textsuperscript{11}. The risk of serious complications is lower if embolization is duly performed and in most cases, as in our series, patients are discharged after short hospitalization.

**Figure 4 (A, B, Γ):** Selective right renal artery angiography in two right kidney RCC sites pre-(A, B) and post-chemoembolization (Γ). The early arterial phase reveals pathologic vascularization with new spiral vessels, more evident in the sizeable lower pole tumor (empty arrows) and subtle in the smaller upper pole tumor (arrow). A later image study (B) showed extensive arteriovenous communications (AVC) in the lower pole tumor, with early opacification of the renal vein (*) and the inferior vena cava (IVC) (**). After the embolization with coils and microspheres (Γ), we observe neovascularization and AVCs elimination.

**Conclusions**

Currently available data suggest that RCC embolization is a relatively well-tolerated treatment option in patients with unresectable renal tumors or patients unfit for surgery or patients who do not wish to undergo a surgical procedure to palliate local symptoms and
improve their clinical status. Especially in elderly patients, radical nephrectomy (RN) may cause significant pre- and post-operative morbidity while in certain cases it also does not allow the application of a systemic treatment. Consequently, renal artery embolization seems to be a safe alternative for the aged patients compared to RN due to its low morbidity and limited range of complications.

References


