**Name of journal: World Journal of Clinical Urology**

**ESPS Manuscript NO: 10900**

**Columns: REVIEW**

Spontaneous regression of renal cell carcinoma: Reality or myth?

Maruschke M *et al.* Spontaneous regression of renal cancer

Matthias Maruschke, Aristotelis G Anastasiadis, Oliver W Hakenberg

**Matthias Maruschke, Aristotelis G Anastasiadis, Oliver W Hakenberg,** Department of Urology, University of Rostock, 18055 Rostock, Germany

**Author contributions:** Maruschke M performed the literature search in the PubMed Database and wrote the manuscript; Anastasiadis AG was actively involved in editing the manuscript; Hakenberg OW was also involved in editing and supervising the manuscript.

**Correspondence to: Matthias Maruschke, MD,** Department of Urology, University of Rostock, Ernst-Heydemann-Strasse 6, 18055 Rostock, Germany. matthias.maruschke@med.uni-rostock.de

**Telephone:** +49-381-4947834 **Fax:** +49-381-4947802

**Received:** April 24, 2014 **Revised:** June 29, 2014

**Accepted:** August 27, 2014

**Published online:**

**Abstract**

Spontaneous regression of a malignant tumor is a very rare phenomenon. Renal cell carcinoma (RCC) is an aggressive malignancy with an often unpredictable behaviour. The incidence of spontaneous regression in metastatic RCC has been estimated to lie between < 1% and 7%. The spontaneous regression of a primary RCC has been reported much less commonly. Our literature review assesses the published literature concerning spontaneous regression of either primary or metastatic RCC. In order to examine this phenomenon in more detail we performed a literature search in the PubMed Database using the Keywords “Renal cell carcinoma”, “metastatic disease”, and “spontaneous regression” and included reports from the last 100 years. The incidence of spontaneous regressions in RCC has always been considered a special feature of RCC compared to other solid malignancies. The majority of case reports of spontaneously regressed RCC describe the regression of metastases after nephrectomy rather than the spontaneous regression of a primary tumor. In cases of reported regression of metastatic RCC, this mostly applied to pulmonary lesions. As possible reasons for spontaneous regressions host immune defense mechanisms against metastatic RCC tissue following nephrectomy are discussed as important factor. RCC is known to be highly immunogenic and the possible existence of cytotoxic serum factors and tumor-specific surface antigens may trigger a cell-mediated cytotoxicity as an immunological basis for regression. Histological verification of supposed regression of a primary tumor may cause diagnostic difficulties, since large central areas of necrosis and cystic lesions of the tumor can occur simultaneously. The well-known phenomenon of necrosis in a fast growing RCC at the time of nephrectomy must not be confused with true spontaneous regression. Therefore, in our opinion such reported cases of supposed partial spontaneous regressions of primary RCCs are highly questionable. Most cases of spontaneous regression of RCC metastases have been reported after nephrectomy as the only treatment. Debulking by tumor nephrectomy then gives the immune system the chance to cope effectively with the remaining much lower quantity of tumour antigens. However, the mechanisms leading to spontaneous regression of metastatic lesions after cytoreductive nephrectomy are still poorly understood.

© 2014 Baishideng Publishing Group Inc. All rights reserved.

**Key words**: Renal cell carcinoma; Spontaneous regression; Primary renal cell carcinoma; Metastatic renal cell carcinoma lesions; Cytoreductive nephrectomy

**Core tip:** Renal cell carcinoma (RCC) is an aggressive malignancy, which, from an immunological point of view, is highly variable. In the era of immunotherapy for metatstatic RCC with interferon or interleukin it was always emphasized that spontaneous remissions of RCC, although comparatively rare, do occur and support the use of immunological therapies in metastatic disease. However, we suspected that this frequently cited occurrence of spontaneous remissions is more legend than reality. We therefore undertook an extensive literature search and included reports from the last 100 years in order to evaluate the scientific evidence describing spontaneous regressions of primary or metastatic RCC.

Maruschke M, Anastasiadis AG, Hakenberg OW.Spontaneous regression of renal cell carcinoma: Reality or myth? *World J Clin Urol* 2014; In press

**Introduction**

Spontaneous regression of a malignant tumor must by necessity be considered a very rare phenomenon. One of the first reported cases was that of a soft tissue sarcoma described by Coley in 1893[1]. In a historic study from 1918, 302 cases of spontaneous tumor regressions were described with only one case of a renal tumour among them[2].
 RCC is an aggressive malignancy with an often unpredictable behaviour. At the time of diagnosis, about one third of all patients will already have metastases and another third will develop metachronic metastatic disease after surgery[3].

As early as 1928, Bumpus reported the first case of a spontaneous regression of metastatic RCC[4]. Further reports of spontaneous regressions of metastatic RCC have mostly been those of pulmonary RCC metastases, which supposedly regressed after radical nephrectomy. The incidence of spontaneous regression in metastatic RCC has been estimated to lie between < 1% and 7%[5, 6]. However, the spontaneous regression of metastatic RCC lesions has also been reported for brain, bone, adrenal and liver metastases[7].

The spontaneous regression of a primary RCC has been reported much less commonly. However, underlying hypothetical mechanisms for spontaneous regression, which have been mentioned in the literature include humoral, immunological and vascular factors, *e.g.,* autoinfarction[8, 9].

In the reported cases of spontaneous regression, the duration of disease remission is either relatively short or has not been reported at all. The longest reliably observed durations of regression of metastatic RCC lasted for 10 years[10] and for over 20 years[5]. Our literature review assesses the published literature concerning spontaneous regression of either primary or metastatic RCC.

**LITERATURE SEARCH**

A literature search was performed in the PubMed Database using the Keywords “Renal cell carcinoma”, “metastatic disease”, and “spontaneous regression” and included reports from the last 100 years.

**research**

Spontaneous regression of a malignant tumor or its metastases has been defined as a partial or total disappearance of disease without any treatment or induced by local treatments or interventions like embolisation of the primary tumor. The incidence of spontaneous regressions in RCC has usually been reported to be about 1% and this has always been considered a special feature of RCC compared to other solid malignancies. However, the natural course of RCC is not always predictable and includes spontaneous regression of pulmonary metastases following nephrectomy, prolonged survival and stable disease, late relapse after nephrectomy and poor long term outcome despite spontaneous regression[11]. Spontaneous regression is not synonymous with cure, as later recurrences have been reported[12, 13]. Thus, a patient cannot be considered cured even if spontaneous regression is suspected if an RCC has been diagnosed[14].

***Possible causes of spontaneous regression***

Following nephrectomy, it is conceivable that host immune defense mechanisms against metastatic RCC tissue may be activated. Everson *et al*[12] in 1966 postulated such an immune mechanism as the most important factor for spontaneous regression of cancer.

Clinical observations seem to support this hypothesis and several examples for the relationship between neoplastic disease and the function of the immune system exist such as the incidence of lymphomas in patients with AIDS or after organ transplantation, the regression of Kaposi´s sarcoma after withdrawal of immunosuppressive therapy[15-18] and the generally increased risk of cancer development with immunosuppression after organ transplantation[19]. As a possible reason some authors postulated a lack of immuno-surveillance of virus-transformed cells by strong immunosuppression. That may lead to an increased frequency of viral infections and/or virus-induced malignancies. Nevertheless, other types of malignant tumors, which are not associated with viral infections, are frequently increased in transplant recipients, too, in dependence of the duration of exposure to immunosuppression[19].

RCC is known to be highly immunogenic and the possible existence of cytotoxic serum factors and tumor-specific surface antigens may trigger a cell mediated cytotoxicity as an immunological basis for regression[20, 21]. The majority of case reports of spontaneously regressed RCC describe the regression of metastases after nephrectomy rather than the spontaneous regression of a primary tumor. In malignant melanoma, studies analyzing the T-cell response in regressive primary melanoma in comparison to the metastatic lesions have found a major difference in the number of T-cells in the regressed primary and in metastatic lesions[22].

In cases of reported regression of metastatic RCC, this mostly applied to pulmonary lesions. The constant antigenic stimulation to which the lungs are exposed and the high quantities of macrophages, lymphocytes and immunoglobulin IgA present in pulmonary tissue have been discussed as possible factors explaining such a phenomenon[23-25]. In contrast, the spontaneous regression of brain metastases has rarely been reported and this has been explained with the blood-brain-barrier limiting an immune response because of a lack of lymphocytes infiltrating the brain tissues compared to other organs and tissues[26]. Thus, hypotheses explaining observed immunological responses against malignant lesions in different sites are available.

This theory of an underlying immune mechanism has been proposed by several authors[27, 28]. A remarkable report is that by Horn *et al*[27] (1971) about the induction of an RCC regression in a patient with metastatic disease after the transfusion plasma from another patient of the same family who had experienced spontaneous regression. The authors suggested “some sort of host resistance” in this case, mainly a plasma-related transfer factor, an interferon-like agent or a kind of cytotoxic antibody or a substance mediating cellular immunity[27].

In contrast, the generally poor response of metastatic RCC to immunotherapy is perhaps an argument not supporting the general importance of immunological mechanisms.

From reported experience with other maligancies which have undergone spontaneous regression (neuroblastoma, malignant melanoma, malignant lymphoma and leukemias), several other factors have been proposed as underlying mechanisms such as growth factors and/or cytokines, the induction of differentiation, endocrine mechanisms, the elimination of a carcinogen, tumor necrosis, apoptosis and/or the inhibition of angiogenesis and epigenetic mechanisms[29]. This number of proposed mechanisms just underscores the fact very little is actually known about spontaneous regression and/or that different mechanisms may be of importance in different cases[10, 29, 30]. For example, cytokine production by the tumor itself or by host tissue has been postulated to be involved in regressions of RCC because in one reported case of regressed intrathoracic metastases elevated serum levels of IL-2 receptor were reported[31].

Necrosis and apoptosis both occur in RCC and result in cell death. Gross central tumour necrosis is often clinically and pathologically seen in large and rapidly growing RCCs. This is usually considered as indicating that the rapid growth outgrowths the tumour’s blood supply. Interestingly, synchronous necrosis within the primary tumor and in the metastatic lesions of RCC seems to be very rare. Bos *et al*[25] (1996) reported such a case of RCC with a caval thrombus and the spontaneous regression of pulmonary metastases. After resection of the primary tumor and the thrombus, histological examination verified necrosis at both sites.

Apoptosis, programmed cell death, has also been suggested to be an underlying mechanism of spontaneous regression in RCC. Pansera[31] (1992) postulated spontaneous RCC regression to be a re-expression of cell death programs typical for renal tissues since pronephros and mesonephros undergo complete regression during embryogenic renal development. Such an embryological cell death program could hypothetically be reactivated in immature RCC tissue. Indeed, the manifestation of embryological cell characteristics does occur in many neoplasms[32]. This phenomenon of morphological similarities between growing tissues, like embryological and cancer cells has its reasoning in a common origin from a precursor stem cell. Thus, spontaneous regression of RCC may be explained as a kind of re-expression of embryonic features by adult carcinoma[32].

***Histological verification of regression***

**In a primary RCC:** Histological verification of supposed regression of a primary tumor may cause diagnostic difficulties, since large central areas of necrosis and cystic lesions of the tumor can occur simultaneously. Therefore, the differential diagnosis of a spontaneously regressed RCC should include inflammatory lesions of the kidney, *e.g.,* xanthogranulomatous pyelonephritis, sinus histiocytosis and tuberculosis or malakoplakia. This requires an extensive tissue sampling by the pathologist to confirm or refute the diagnosis of spontaneous regression of an RCC[33].

In our review of the literature we found only 7 reported cases of partial or total spontaneous regression of primary RCCs (Table 1). However, in most of these seven cases the regressions were not unequivocally confirmed.

The first documented case of a total spontaneous regression of a primary RCC was reported by Choi *et al*[34] in 1986. The authors diagnosed a left sided renal tumor and performed a nephrectomy. Histologic examination revealed a cyst-like capsule with coagulated blood, necrotic tissue, calcifications and a cluster of tumor cells, which were classified as a spontaneously regressed primary RCC.

Hamid *et al*[33] in 1998 described two similar cases, one with a cystic cavity of the kidney “containing necrotic debris and brown fluid occupying virtually the whole of the specimen” and “occasional foci of viable renal cell carcinoma …seen in the capsular area”. These findings were deemed to represent spontaneous regression by the authors. However, the differential diagnosis must include a developing RCC within a cystic renal lesion with previous hemorrhage. The second case reported by Hamid and Poller should also be viewed critically. There they found “an extensively involuted/hyalinised lesion with extensive metaplastic ossification and also foci of dystrophic calcification” and, again, “occasional foci of cells with clear cytoplasm”. Neither of these two case reports included any follow-up information at all[33].

More stringently, spontaneous regression of an RCC or its metastases should be defined as a partial or complete regression of a renal neoplasm which has been histologically confirmed first and then regressed either without treatment or sometimes following an intervention, *e.g.,* cytoreductive nephrectomy. It is important to note that it is possible to find necrosis in a fast growing RCC at the time of nephrectomy and this well-known phenomenon must not be confused with true spontaneous regression. However, some authors do consider such a necrosis as a partial regression[35, 36]. Thus, in our opinion such reported cases of supposed spontaneous regressions of primary RCCs are highly questionable (Table 1).

**In metastatic RCC lesions:** In all, we found 94 reported cases of spontaneous regression of metastatic lesions in patients with an RCC (Table 2). Most of these reports concern pulmonary metastases (75 cases) and only a few other sites: pleura and mediastinum (3), liver (4), pancreas (1), brain (3), bone (5), eyes (2) and skin (1) (Table 2). Most of these case reports give no histological verification of the supposedly metastatic lesions. Thus, the diagnosis of spontaneous regression was based on changes in size on imaging which therefore cannot be considered as a proof beyond doubt.

Kavoussi *et al*[37] reported a rate of regression of 20% based on diagnosis by cytology. However, Davis *et al* found a regression of pulmonary RCC metastases in only 3/14 documented cases, *i.e*., unrelated to any kind of treatment including nephrectomy[38].

In evaluating spontaneous regression of a primary tumor as well as metastatic lesions, histological verification can be a diagnostic challenge. Patients with advanced metastatic disease are often not in good general condition for any surgical or interventional procedures. Edwards *et al*[35] (1996) pointed out that fine needle biopsy carries a risk of gross bleeding due to blood coagulation potentially affected by paraneoplastic mechanisms. Furthermore, CT-guided biopsies may be unsuccessful in rendering good histologic reports because of insufficient sample size.

In case of eye or brain lesions, cytological or histological verification is even more difficult and dangerous. Thus, in clinical practice such procedures are usually avoided when the primary tumor has been histologically confirmed as an RCC[39- 41].

Thus, in cases without convincing histological evidence of pulmonary RCC metastases, several other benign conditions must be considered in the differential diagnosis, such as fungal or mycobacterial infections, sarcoidosis, Wegener granulomatosis and vasculitic lesions which can all appear as pulmonary lesions and regress later[38]. In the pre-CT era, the misinterpretation of radiological findings in conventional chest X-ray studies may have been more common than appreciated at the time. Thus, cases diagnosed as spontaneous regression of RCC metastases in the lungs by chest x-ray only should also be regarded with caution. Furthermore, even cases of pulmonary RCC lesions by cytology or even histology which then had spontaneous regression diagnosed by chest X-ray only must be questioned in retrospect[42]. Embolisation of the lung or a pulmonary segment by tumor thrombi from the renal vein may cause regional pulmonary infarction, which may have the radiological appearance of metastatic lesions. The disappearance of these findings after improvement of inflammatory lesions close to such an embolus could also be misinterpreted as a spontaneous regression[43, 44].

***Cytoreductive nephrectomy***

More than 40 years ago, Markewitz *et al*[45] advocated a palliative nephrectomy only to be considered in individually selected cases with careful evaluation of the potential benefit. However, since then a markedly longer survival has been shown in patients with RCC after nephrectomy and metastasectomy[46]. Therefore, the concept of cytoreductive nephrectomy should today be taken into consideration in all patients with metastatic RCC when the short-term outcome of the surgical procedure can be predicted to be acceptable[47].

Indeed, most cases of spontaneous regression of RCC metastases have been reported after nephrectomy as the only treatment. Two possible hypotheses have been put forward as explanations for this phenomenon:

First, a dissemination of tumor cells into the systemic circulation and the lymphatic system induced by the surgical procedure results in a large and ubiquitous presentation of tumor antigen and this may initiate a strong antitumoral immune response by the host. Secondly, because of the mass of tumour antigen is located in the primary tumor, debulking by tumor nephrectomy then gives the immune system the chance to cope effectively with the remaining much lower quantity of tumour antigens and thus to mount an effective antineoplastic response[13, 14].

Although the morbidity and mortality of nephrectomy should always be taken into consideration, a palliative cytoreductive nephrectomy in metastatic RCC may also be beneficial for other reasons: in terms of the prevention of tumor toxicity, for the correction of hypercalcaemia and for the improvement of local symptoms, such as pain or hematuria[40, 51-53].

Regression has also been described to occur after other local treatments such as radiotherapy or embolisation of the primary tumor[7, 37, 38, 48-50].

**CONCLUSION**

Spontaneous regression in renal cell carcinoma is very rare and there probably has been an overreporting in the literature. However, it has been described plausibly in metastatic RCC sites – mostly pulmonary – and then mostly after nephrectomy, thus supporting the concept of cytoreductive nephrectomy. Despite several plausible hypotheses, the mechanisms leading to spontaneous regression of metastatic lesions after cytoreductive nephrectomy are still poorly understood.

**REFERENCES**

1 **Coley WB**. The treatment of malignant tumors by repeated inoculations of erysipelas. With a report of ten original cases. 1893. *Clin Orthop Relat Res* 1991; : 3-11 [PMID: 1984929 DOI: 10.1097/00000441-189305000-00001]

2 **Rohdenburg GL**. Fluctuations in the growth energy of malignant tumors in man, with especial reference to spontan recession. *J Cancer Res* 1918, **3:** 193

3 **Katz SE**, Schapira HE. Spontaneous regression of genitourinary cancer--an update. *J Urol* 1982; **128**: 1-4 [PMID: 7050408]

4 **Bumpus HC,Jr**. The apparent disappearance of pulmonary metastasis in a case of hypernephroma following nephrectomy. *J Urol* 1928, **20:** 185

5 **Snow RM**, Schellhammer PF. Spontaneous regression of metastatic renal cell carcinoma. *Urology* 1982; **20**: 177-181 [PMID: 7112827 DOI: 10.1016/0090-4295(82)90356-9]

6 **Oliver RT**, Nethersell AB, Bottomley JM. Unexplained spontaneous regression and alpha-interferon as treatment for metastatic renal carcinoma. *Br J Urol* 1989; **63**: 128-131 [PMID: 2702395 DOI: 10.1111/j.1464-410X.1989.tb05147.x]

7 **Lokich J**. Spontaneous regression of metastatic renal cancer. Case report and literature review. *Am J Clin Oncol* 1997; **20**: 416-418 [PMID: 9256902 DOI: 10.1097/00000421-199708000-00020]

8 **Kobayashi K**, Sato T, Sunaoshi K, Takahashi A, Tamakawa M. Spontaneous regression of primary renal cell carcinoma with inferior vena caval tumor thrombus. *J Urol* 2002; **167**: 242-243 [PMID: 11743317 DOI: 10.1016/S0022-5347(05)65424-9]

9 **Sufrin G**, Murphy GP. Renal adenocarcinoma. *Urol Surv* 1980; **30**: 129-144 [PMID: 7445322]

10 **Christophersen AO**, Lie AK, Fosså SD. Unexpected 10 years complete remission after cortisone mono-therapy in metastatic renal cell carcinoma. *Acta Oncol* 2006; **45**: 226-228 [PMID: 16546876 DOI: 10.1080/02841860500400995]

11 **Chang KC**, Chan KL, Lam CW. Spontaneous regression of renal cell carcinoma metastases. *Hong Kong Med J* 1999; **5**: 72-75 [PMID: 11821572]

12 **Everson TC**, Cole WH. Spontaneous regression of cancer. Philadelphia: Saunders Co, 1966 p.11-87

13 **Silber SJ**, Chen CY, Gould F. Regression of Metastases after Nephrectomy for Renal Cell Carcinoma. *Br J Urol* 1975; **47**: 259-261 [PMID: 1139117 DOI: 10.1111/j.1464-410X.1975.tb03959.x]

14 **de Riese W**, Goldenberg K, Allhoff E, Stief C, Schlick R, Liedke S, Jonas U. Metastatic renal cell carcinoma (RCC): spontaneous regression, long-term survival and late recurrence. *Int Urol Nephrol* 1991; **23**: 13-25 [PMID: 1938215 DOI: 10.1007/BF02549723]

15 **Salloum E**, Cooper DL, Howe G, Lacy J, Tallini G, Crouch J, Schultz M, Murren J. Spontaneous regression of lymphoproliferative disorders in patients treated with methotrexate for rheumatoid arthritis and other rheumatic diseases. *J Clin Oncol* 1996; **14**: 1943-1949 [PMID: 8656264]

16 **Rabkin CS**, Hilgartner MW, Hedberg KW, Aledort LM, Hatzakis A, Eichinger S, Eyster ME, White GC, Kessler CM, Lederman MM. Incidence of lymphomas and other cancers in HIV-infected and HIV-uninfected patients with hemophilia. *JAMA* 1992; **267**: 1090-1094 [PMID: 1735926 DOI: 10.1001/jama.1992.03480080060027]

17 **Penn I**. Cancers complicating organ transplantation. *N Engl J Med* 1990; **323**: 1767-1769 [PMID: 2247108 DOI: 10.1056/NEJM199012203232510]

18 **Tebbe B**, Mayer-da-Silva A, Garbe C, von Keyserlingk HJ, Orfanos CE. Genetically determined coincidence of Kaposi sarcoma and psoriasis in an HIV-negative patient after prednisolone treatment. Spontaneous regression 8 months after discontinuing therapy. *Int J Dermatol* 1991; **30**: 114-120 [PMID: 2001900 DOI: 10.1111/j.1365-4362.1991.tb04222.x]

19 **Dantal J**, Hourmant M, Cantarovich D, Giral M, Blancho G, Dreno B, Soulillou JP. Effect of long-term immunosuppression in kidney-graft recipients on cancer incidence: randomised comparison of two cyclosporin regimens. *Lancet* 1998; **351**: 623-628 [PMID: 9500317 DOI: 10.1016/S0140-6736(97)08496-1]

20 **Montie JE**, Straffon RA, Deodhar SD, Barna B. In vitro assessment of cell-mediated immunity in patients with renal cell carcinoma. *J Urol* 1976; **115**: 239-242 [PMID: 1255882]

21 **Ueda R**, Shiku H, Pfreundschuh M, Takahashi T, Li LT, Whitmore WF, Oettgen HF, Old LJ. Cell surface antigens of human renal cancer defined by autologous typing. *J Exp Med* 1979; **150**: 564-579 [PMID: 479762 DOI: 10.1084/jem.150.3.564]

22 **Carcelain G**, Rouas-Freiss N, Zorn E, Chung-Scott V, Viel S, Faure F, Bosq J, Hercend T. In situ T-cell responses in a primary regressive melanoma and subsequent metastases: a comparative analysis. *Int J Cancer* 1997; **72**: 241-247 [PMID: 9219827 DOI: 3.0.CO; 2-R']

23 **Freed SZ**, Halperin JP, Gordon M. Idiopathic regression of metastases from renal cell carcinoma. *J Urol* 1977; **118**: 538-542 [PMID: 916044]

24 **Bos SD**, Mensink HJ. Spontaneous caval tumor thrombus necrosis and regression of pulmonary lesions in renal cell cancer. *Scand J Urol Nephrol* 1996; **30**: 489-492 [PMID: 9008031 DOI: 10.3109/00365599609182329]

25 **Boasberg PD**, Eilber FR, Morton DL. Immunocompetence and spontaneous regression of metastatic renal cell carcinoma. *J Surg Oncol* 1976; **8**: 207-210 [PMID: 933543 DOI: 10.1002/jso.2930080304]

26 **Horn L**, Horn HL. An immunological approach to the therapy of cancer? *Lancet* 1971; **2**: 466-469 [PMID: 4105332 DOI: 10.1016/S0140-6736(71)92632-8]

27 **Abubakr YA**, Chou TH, Redman BG. Spontaneous remission of renal cell carcinoma: a case report and immunological correlates. *J Urol* 1994; **152**: 156-157 [PMID: 8201650]

28 **Papac RJ**. Spontaneous regression of cancer: possible mechanisms. *In Vivo* 1998; **12**: 571-578 [PMID: 9891219]

29 **Lekanidi K**, Vlachou PA, Morgan B, Vasanthan S. Spontaneous regression of metastatic renal cell carcinoma: case report. *J Med Case Rep* 2007; **1**: 89 [PMID: 17877824 DOI: 10.1186/1752-1947-1-89]

30 **MacManus MP**, Harte RJ, Stranex S. Spontaneous regression of metastatic renal cell carcinoma following palliative irradiation of the primary tumour. *Ir J Med Sci* 1994; **163**: 461-463 [PMID: 7529223 DOI: 10.1007/BF02940567]

31 **Pansera F**. Regression in renal cell carcinoma as re-expression of cell death in kidney development. *Perspect Biol Med* 1992; **35**: 416-421 [PMID: 1502003]

32 **Hamid Y**, Poller DN. Spontaneous regression of renal cell carcinoma: a pitfall in diagnosis of renal lesions. *J Clin Pathol* 1998; **51**: 334-336 [PMID: 9659251 DOI: 10.1136/jcp.51.4.334]

33 **Choi SK**, Chang SK, Lee JM, Jung WH, Park CI. Spontaneous regression of primary renal cell carcinoma--a case report. *Yonsei Med J* 1986; **27**: 314-317 [PMID: 3564545]

34 **Edwards MJ**, Anderson JA, Angel JR, Harty JI. Spontaneous regression of primary and metastatic renal cell carcinoma. *J Urol* 1996; **155**: 1385 [PMID: 8632583 DOI: 10.1016/S0022-5347(01)66275-X]

35 **Lacquaniti S**, Pierconti F, Servello C, Pisanti F, Destito A. Spontaneous partial fibrotic regression of a primary renal carcinoma: a case report. *Arch Ital Urol Androl* 1999; **71**: 35-36 [PMID: 10193022]

36 **Kavoussi LR**, Levine SR, Kadmon D, Fair WR. Regression of metastatic renal cell carcinoma: a case report and literature review. *J Urol* 1986; **135**: 1005-1007 [PMID: 3959224]

37 **Davis SD**, Koizumi JH, Pitts WR. Spontaneous regression of pulmonary metastases from renal cell carcinoma. *Urology* 1989; **33**: 141-144 [PMID: 2916288 DOI: 10.1016/0090-4295(89)90014-9]

38 **Langmann G**, Müllner K. Spontaneous regression of a choroidal metastasis from renal carcinoma. *Br J Ophthalmol* 1994; **78**: 883 [PMID: 7848991 DOI: 10.1136/bjo.78.11.883]

39 **Guthbjartsson T**, Gíslason T. Spontaneous regression of brain metastasis secondary to renal cell carcinoma. *Scand J Urol Nephrol* 1995; **29**: 215-217 [PMID: 7569801 DOI: 10.3109/00365599509180565]

40 **Hammad AM**, Paris GR, van Heuven WA, Thompson IM, Fitzsimmons TD. Spontaneous regression of choroidal metastasis from renal cell carcinoma. *Am J Ophthalmol* 2003; **135**: 911-913 [PMID: 12788144 DOI: 10.1016/S0002-9394(02)01973-6]

41 **Merz VW**, Looser C, Kraft R, Studer UE. Pseudoregression of pulmonary metastasis after nephrectomy for renal carcinoma. *Br J Urol* 1993; **71**: 751-753 [PMID: 8343906 DOI: 10.1111/j.1464-410X.1993.tb16081.x]

42 **Mage P**, Ballanger P, Lakdja F, Guibert JL, Vincent J, Chomy P, Lamarche P. [Spontaneous regression of pulmonary images interpreted as metastases of kidney cancer. Apropos of 2 cases]. *Ann Urol (Paris)* 1986; **20**: 271-274 [PMID: 3740808]

43 **Wagner JR**, Merino MJ, Pass HI, Linehan WM, Walther MM. Pulmonary infarcts can mimic pulmonary metastases from renal cancer. *J Urol* 1997; **158**: 1688-1690 [PMID: 9334579 DOI: 10.1016/S0022-5347(01)64096-5]

44 **Markewitz M**, Taylor DA, Veenema RJ. Spontaneous regression of pulmonary metastases following palliative nephrectomy. Case report. *Cancer* 1967; **20**: 1147-1154 [PMID: 4165252 DOI: 3.0.CO; 2-K']

45 **van der Poel HG**, Roukema JA, Horenblas S, van Geel AN, Debruyne FM. Metastasectomy in renal cell carcinoma: A multicenter retrospective analysis. *Eur Urol* 1999; **35**: 197-203 [PMID: 10072620 DOI: 10.1159/000019849]

46 **Van Poppel H**, Baert L. Nephrectomy for metastatic renal cell carcinoma and surgery for distant metastases. *Acta Urol Belg* 1996; **64**: 11-17 [PMID: 8701800]

47 **Gutiérrez Fuentes JA**, Fernández Remis JE, Silmi Moyano A, Tomé Paule C. [Spontaneous regression of the metastasis of renal carcinoma]. *Rev Clin Esp* 1980; **158**: 163-166 [PMID: 7433731]

48 **Fairlamb DJ**. Spontaneous regression of metastases of renal cancer: A report of two cases including the first recorded regression following irradiation of a dominant metastasis and review of the world literature. *Cancer* 1981; **47**: 2102-2106 [PMID: 7226102 DOI: 3.0.CO; 2-K']

49 **Thoroddsen A**, Gudbjartsson T, Geirsson G, Agnarsson BA, Magnusson K. Spontaneous regression of pleural metastases after nephrectomy for renal cell carcinoma--a histologically verified case with nine-year follow-up. *Scand J Urol Nephrol* 2002; **36**: 396-398 [PMID: 12487751 DOI: 10.1080/003655902320783971]

50 **Montie JE**, Stewart BH, Straffon RA, Banowsky LH, Hewitt CB, Montague DK. The role of adjunctive nephrectomy in patients with metastatic renal cell carcinoma. *J Urol* 1977; **117**: 272-275 [PMID: 65479]

51 **Middleton AW**. Indications for and results of nephrectomy for metastatic renal cell carcinoma. *Urol Clin North Am* 1980; **7**: 711-717 [PMID: 6161461]

52 **Garfield DH**, Kennedy BJ. Regression of metastatic renal cell carcinoma following nephrectomy. *Cancer* 1972; **30**: 190-196 [PMID: 5040742 DOI: 3.0.CO; 2-H']

53 **Hall FJ**. Hypernephroma. *Arch Int Med* 1908; **4**: 355-391. [DOI: 10.1001/archinte.1908.00050090060003]

54 **Meinders AE**. Spontaneous regression of (presumably) pulmonary metastases in a patient with a renal clear-cell carcinoma. A case report. *Folia Med Neerl* 1971; **14**: 53-61 [PMID: 5559123]

55 **Vizel M**, Oster MW, Austin JH. Spontaneous regression of a pulmonary metastasis after nephrectomy for renal cell carcinoma. *J Surg Oncol* 1979; **12**: 175-180 [PMID: 491686 DOI: 10.1002/jso.2930120212]

56 **Mohr SJ**, Whitesel JA. Spontaneous regression of renal cell carcinoma metastases after preoperative embolization of primary tumor and subsequent nephrectomy. *Urology* 1979; **14**: 5-8 [PMID: 452221 DOI: 10.1016/0090-4295(79)90201-2]

57 **Nakano E**, Sonoda T, Fujioka H, Okuyama A, Matsuda M, Osafune M, Takaha M. Spontaneous regression of pulmonary metastases after nephrectomy for renal cell carcinoma. *Eur Urol* 1984; **10**: 212-213 [PMID: 6723742]

58 **Barré C**, Vérine JL, Régnier J, Enon B, Houssin A, Chaigné P, Soret JY. [Spontaneous regression of regressive pulmonary metastases from kidney cancer. Myth or reality? Apropos of 2 cases]. *Ann Urol (Paris)* 1986; **20**: 275-279 [PMID: 3740809]

59 **Eissler M**. [Spontaneous regression of lung metastasis in renal cell carcinoma with expectoration of a part of the metastasis]. *Med Klin (Munich)* 1989; **84**: 118-119 [PMID: 2710052]

60 **Omland H**, Fosså SD. Spontaneous regression of cerebral and pulmonary metastases in renal cell carcinoma. *Scand J Urol Nephrol* 1989; **23**: 159-160 [PMID: 2756362 DOI: 10.3109/00365598909180834]

61 **Vogelzang NJ**, Priest ER, Borden L. Spontaneous regression of histologically proved pulmonary metastases from renal cell carcinoma: a case with 5-year followup. *J Urol* 1992; **148**: 1247-1248 [PMID: 1404646]

62 **Palmer MA**, Viswanath S, Desmond AD. Spontaneous regression of metastatic renal cell carcinoma. *J R Soc Med* 1993; **86**: 113-114 [PMID: 8433295]

63 **Garcia-Del-Muro X**, Cardenal F, Romagosa V, Gil M. Sarcomatoid renal cell carcinoma: a case of spontaneous regression of metastases. *Eur Urol* 1993; **24**: 300-301 [PMID: 8375455]

64 **Czaplicki M**, Malewski AW, Kuzaka B, Mayzner-Zawadzka E. [The puzzle of spontaneous regression of pulmonary metastasis of renal carcinoma (after many years of observing the patient)]. *Pol Tyg Lek* 1993; **48**: 485-487 [PMID: 8170818]

65 **Marcus SG**, Choyke PL, Reiter R, Jaffe GS, Alexander RB, Linehan WM, Rosenberg SA, Walther MM. Regression of metastatic renal cell carcinoma after cytoreductive nephrectomy. *J Urol* 1993; **150**: 463-466 [PMID: 8326579]

66 **Rauh S**, Duhem C, Ries F, Dicato M, Lamy S, Lens V. [Spontaneous regression of pulmonary metastases in renal cancer]. *Bull Soc Sci Med Grand Duche Luxemb* 1998; **135**: 39-42 [PMID: 9868831]

67 **Sánchez-Ortiz RF**, Tannir N, Ahrar K, Wood CG. Spontaneous regression of pulmonary metastases from renal cell carcinoma after radio frequency ablation of primary tumor: an in situ tumor vaccine? *J Urol* 2003; **170**: 178-179 [PMID: 12796677 DOI: 10.1097/01.ju.0000070823.38336.7b]

68 **Mims MM**, Christenson B, Schlumberger FC, Goodwin WE. A 10-year evaluation of nephrectomy for extensive renal-cell carcinoma. *J Urol* 1966; **95**: 10-15 [PMID: 5903858]

69 **Doolittle KH**. Spontaneous remission of solitary bony metastasis after removal of the primary kidney adenocarcinoma. *J Urol* 1976; **116**: 803-804 [PMID: 1003657]

70 **Kerbl K**, Pauer W. Spontaneous regression of osseous metastasis in renal cell carcinoma. *Aust N Z J Surg* 1993; **63**: 901-903 [PMID: 8216071 DOI: 10.1111/j.1445-2197.1993.tb00368.x]

71 **Nakajima T**, Suzuki M, Ando S, Iida T, Araki A, Fujisawa T, Kimura H. Spontaneous regression of bone metastasis from renal cell carcinoma; a case report. *BMC Cancer* 2006; **6**: 11 [PMID: 16412235 DOI: 10.1186/1471-2407-6-11]

72 **Kallmeyer JC**, Dittrich OC. Spontaneous regression of metastases in a case of bilateral renal cell carcinoma. *J Urol* 1992; **148**: 138-140 [PMID: 1613856]

73 **Deweerd JH**, Hawthorne NJ, Adson MA. Regression of renal cell hepatic metastasis following removal of primary lesions. *J Urol* 1977; **117**: 790-792 [PMID: 875160]

74 **Ritchie AW**, Layfield LJ, deKernion JB. Spontaneous regression of liver metastasis from renal carcinoma. *J Urol* 1988; **140**: 596-597 [PMID: 3411682]

75 **Wyczólkowski M**, Klima W, Bieda W, Walas K. Spontaneous regression of hepatic metastases after nephrectomy and metastasectomy of renal cell carcinoma. *Urol Int* 2001; **66**: 119-120 [PMID: 11223759 DOI: 10.1159/000056586]

76 **Altschuler EL**, Ray A. Spontaneous regression of a pancreatic metastasis of a renal cell carcinoma. *Arch Fam Med* 1998; **7**: 516-517 [PMID: 9821824 DOI: 10.1001/archfami.7.6.516]

77 **Hensiek AE**, Kellerman AJ, Hill JT. Spontaneous regression of a solitary cerebral metastases in renal carcinoma followed by meningioma development under medroxyprogesterone acetate therapy. *Br J Neurosurg* 2000; **14**: 354-356 [PMID: 11045205 DOI: 10.1080/026886900417388]

**P-Reviewer:** Shoji S, Vieyra A **S-Editor:** Wen LL **L-Editor: E-Editor:**

**Table 1 Regression of primary** **renal cell carcinoma**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Case** | **Year** | **Type of regression** | **Histology documented** | **Follow up** |
|  |  |  |  | **(interval)** |
| Hall[54]  | 1908 | total regression (?) | Entirely nectrotic tumor | Not given |
|   |  |  |  |   |
| ChoiKang *et al*[34] | 1986 | total regression (?) | Cyst-like capsule with necrotic tissue |   |
|   |  |  | Calcifications and a cluster of tumor cells …" |   |
|   |  |  |  |   |
| Edwards *et al*[35] | 1996 | partial regression | Residual RCC with marked fibrosis  | 36 mo |
|   |  |  | And calcification |   |
|   |  |  |  |   |
| Hamid *et al*[33] | 1998 | "extensive regression" | Extensively hyalinised lesion, also foci | not given |
|   |  |  | Of cells with clear cytoplasm |   |
|   |  |  | Cystic cavity containing necrotic | not given |
|   |  |  | Debris, occasional foci of viable RCC |   |
|   |  |  |  |   |
| Lacquaniti *et al*[36] | 1999 | partial regression | Fibrotic involution ….. | 7 mo |
|   |  |  | With few central areas of RCC" |   |
|   |  |  |  |   |
| Kobayashi *et al*[8] | 2002 | partial regression of primary  |  No  | 2 yr |
|   |  | RCC with inferior V. cava |  |   |
|   |  | tumor thrombus |  |   |
|   |   |   |   |   |

RCC: Renal cell carcinoma.

**Table 2** **Regression of metastases from renal cell carcinoma**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| **Site of**  | **Source** | **Number of**  | **Histological**  | **Follow up**  |  |
| **metastases** |  | **cases** | **documentation** | **(interval)** |  |
|  |  |  |  |  |  |
| **Lung** | Meinders *et al*[55] | 1 | No | 3 yr |  |
|   | Boasberg *et al* [26] | 1 | No | 2.5 yr |  |
|  | cited by Freed *et al* [23] | 45 | 13/45 |   |  |
|   |  | (from 1928 - 1976) |  |   |  |
|   | Vizel *et al* [56] | 1 | No | 11 mo |  |
|   | Mohr *et al*[57] | 1 | No | 22 mo |  |
|   | Snow *et al*[5] | 1 | Yes | 6.5 yr |  |
|   | Nakano *et al* [58] | 1 | No | 8 yr |  |
|  | Barré *et al* [59] | 2 | Yes | 5 yr |  |
|   | Kavoussi *et al* [37] | 1 | Yes (cytologically) | 6 yr |  |
|  | Eissler[60] | 1 | Yes | 7 yr |  |
|  | Omland *et al*[61] | 1 | No | 14 mo |  |
|   | Davis *et al* [38] | 1 | Cytologically | 18 mo |  |
|   | de Riese *et al* [14] | 2 | No | 5,5 - 11 yr |  |
|   | Vogelzang *et al* [62] | 1 | Yes (cytologically) | 5 yr |  |
|   | Palmer *et al* [63] | 1 | No | 15 mo |  |
|   | Garcia-Del-Muro *et al* [64] | 1 | No | 1 yr |  |
|   | Czaplicki *et al* [65] | 1 | Not given | 16 yr |  |
|   | Marcus *et al* [66] | 4 | No | 1 – 4.5 yr |  |
|   | Mac Manus *et al* [31] | 1 | Yes | 9 mo |  |
|   | Bos *et al*[25] | 1 | No | 1 yr |  |
|  | Edwards *et al* [35] | 1 | No | 36 mo |  |
|   | Lokich [7] | 1 | No | 2 yr |  |
|  | Rauh *et al* [67] | 1 | Yes | 8 mo |  |
|   | Chang *et al* [11] | 1 | Yes | 16 mo |  |
|   | Sanchez-Ortiz *et al* [68] | 1 | Yes | 10 mo |  |
|   | Lekanidi *et al* [30] | 1 | No | 5 mo |  |
| **Bone** | Mims *et al* [69] | 1 | Yes | 1 yr |  |
|   | Doolittle *et al* [70] | 1 | Yes | 4 yr |  |
|   | Freed *et al* [23] | 1 | Yes | 10 yr |  |
|  | Kerbl *et al* [71] | 1 | Yes | 13 mo |  |
|   | Nakajima *et al* [72] | 1 | Yes | 8 mo |  |
| **Pleural /** | Kallmeyer *et al* [73] | 1 | Yes | 3 mo |  |
| **mediastinal** | Abubakr *et al* [28] | 1 | Yes | 1.5 yr |  |
|  | Thoroddsen *et al* [50] | 1 | Yes | 9 yr |  |
| **Liver** | Deweerd *et al* 1977[74] | 1 | Yes | 6 mo |  |
|   | Ritchie *et al* [75] | 1 | Yes | 9 mo |  |
|  | Wyczolkowski *et al* [76] | 1 | Yes | 12 mo |  |
|   | Christophersen *et al* [10] | 1 | Yes | 5 yr |  |
| **Pancreatic** | Altschuler *et al* [77] | 1 | Yes | 2.5 yr |  |
| **choroidal** | Langmann *et al* [39] | 1 | No | 6 mo |  |
|  | Hammad *et al* [41] | 1 | No |   |  |
| **Brain** | Omland *et al* [61] | 1 | No | 14 mo |  |
|   | Gudbjartsson *et al*  | 1 | No | 9 yr |  |
|   |  [40] |  |  |   |  |
|  | Hensiek *et al* [78] | 1 | No | 4 yr |  |
| **Skin** | Chang *et al* [11] | 1 | No | 16 mo |  |
|   |   |   |   |   |  |

RCC: Renal cell carcinoma.