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LYMPH NODE DISSECTION, RENAL ARTERY EMBOLIZATION AND OTHER ASPECTS OF THE MANAGEMENT OF RENAL CARCINOMA*

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The standard treatment for renal carcinoma is surgical excision. The exact extent of the nephrectomy is a subject for discussion but the basic surgical procedure is to remove the kidney, its perinephric fat and the fascial envelope. If the tumor is in the lower half of the kidney, the nephrectomy can be achieved by an incision either through the bed of the 12th rib or between the 11th and 12th rib. If the tumor is in the upper half of the kidney, a thoraco-abdominal incision may be preferred. Early access to the renal artery and vein is advocated because of the potential risk of causing neoplastic emboli with mobilization of the renal mass; for most tumors however, the flank incision provides a good safe access. The most debatable part of a nephrectomy for renal carcinoma is whether or not the dissection should include the regional lymph nodes.

Lymph node dissection

The main proponent for a routine lymphadenectomy as part of a radical nephrectomy has been Robson[1] who claimed that the addition of this procedure was the main reason for his improved 5 year survival rate compared with other published series[2] (Table I). Others, however, have been less convinced about the need and the advantages. Pizzocaro et al[3] emphasized the need to distinguish between M1 and M0 patients and in their series, lymph node metastases were very uncommon in T1 and T2 categories and occurred in only 6.8% for all M0 cases compared with 32.4% for M1 cases. The number of cases that might benefit from routine lymph node dissection is therefore very small and the value of this procedure remains in doubt.

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In the Robson classification of renal carcinomas, a stage III tumor is one that involves the regional lymph nodes and/or renal vein or inferior vena cava. It is however, difficult to determine from most reported series the exact proportion of node or vein involvement and, because the latter is not a strong risk factor[4], reports of good stage III survival may be misleading and may not necessarily be attributed to routine lymph node dissection[5].

DeKernion[6] advocated a compromise because he was unwilling to accept the increased morbidity of a radical dissection: he recommended a node dissection from the inferior mesenteric artery to the adrenals, with the aorta the medial border for left sided tumors and the vena cava for right sided tumors.

It is relevant to note that there is a close correlation between the size of the tumor and the incidence of positive regional nodes. Hellsten et al[7] have shown that the occurrence of node metastases is very rare for tumors less than 6.5 cm in diameter. Hulten et al[8] also showed that the spread of lymph nodes was not always in direct continuity with the primary and that iliac and supraclavicular nodes may be positive yet intervening nodes are negative.

The exact role of lymph node dissection may never be finally resolved because it will require a large prospective study using the same staging techniques and patients that are carefully matched for stage, grade and other risk factors.

Renal Artery Embolization

Early reports on the use of renal artery embolization showed a possible clinical use but benefits were not readily accepted[9]. In 1973 Almgard et al[10] described their experience of renal artery occlusion in the management of 19 renal carcinomas. Their technique consisted of autologous muscle suspension injected via a catheter placed in the renal artery. All patients developed a mild fever for the first 24 hours after embolization. Nine of the 19 cases subsequently underwent a nephrectomy and it appears that the mass was reduced in size, that peroperative beleeding was less and that the tumors were more accessible to surgical removal. Four cases were embolized to control hematuria only and this sign gradually disappeared over 1-3 days after embolization. It was hoped that by reducing the amount of tumor either by necrosis alone or combined with surgical removal, the immunological action on the metastases might be facilitated; in 3 of 8 cases treated by embolization alone, the metastases remained unchanged for a surprisingly long time. Interest in the therapeutic effects of renal artery embolization remained hesitant in the following years. A large number of methods for achieving an effective occlusion were described: autologous clot, silastic balls, cyano-acrylate, silicone balloons, alcohol, dura and ethibloc glue were all described. One of the most effective has been the use of gel-foam to occlude the smaller, peripheral vessels and then to occlude the main renal artery with Gianturco coils.

Experience with renal artery embolization in the University Department of Surgery/Urology has been in 3 groups of patients:

1. To facilitate the surgical excision of a renal tumor
2. For palliation only
3. To study the immunological effect of embolization and nephrectomy.

1. Experience with embolization to facilitate nephrectomy has shown that for some tumors the reduced vascularity is a definite advantage[11]. However, this advantage needs to be balanced with the pain or discomfort or fever produced by embolization and many urologists have felt that embolization should be limited to those tumors that have a massive abnormal circulation and that it need not be used as a routine procedure for the many more straightforward tumors. In an attempt to avoid post-embolization symptoms and to simplify the procedure, Mee and Heap[12] recommended that a Schwan - Ganz balloon tipped arterial catheter is used to occlude the renal artery one hour before nephrectomy. Whichever approach is used, it is evident that many urologists in the UK have found embolization to be of limited practical value and some have now stopped the routine use of this procedure[13].

2. The value of renal artery embolization for palliation as suggested by Almgard et al[10] has not been well documented. The collected Edinburgh experience from 1977 to 1982 was 24 cases (unpublished data). The main benefits were the control of hematuria and the relief of pain. However, other benefits were noted in single cases - relief of vena cava obstruction, regression of pulmonary metastases and healed pathological fracture. It can be concluded from this small experience that a useful amount of palliation can be achieved in approximately 50% of cases and that this is a procedure that should be considered for patients with symptomatic advanced tumors.

3. In addition to the reduced vascularity of the renal tumor mass it has also been implied, but never scientifically established, that necrosis of the tumor may have an effect on the immune system[10]. By delaying the time between embolization and removal of the tumor it has been suggested that the patient receives specific active immunotherapy in the form of an auto vaccination[14]. In a single case report Mohr and Whitesel[15] embolized a large renal carcinoma and removed it 7 days later; there followed progressive regression of pulmonary metastases so that 9 months later the lung fields were clear. These authors encouraged the view that the ischemic necrosis presented a large amount of inactivated tumor antigen to the host which then augumented tumor specific immunity. A large study of delayed nephrectomy following embolization in patients with metastatic carcinoma has been reported from the M.D. Anderson Hospital; here 88 of the 100 patients also received post-operative parenteral medroxyprogesterone.

Complete regression of all metastatic lesions occurred in 7 patients, regression greater than 50% in 8 and stabilization for at least one year in 13 patients: an overall response rate of 28%. The most significant improvement occurred in those patients with parenchymal lung metastases; those with other metastatic lesions had a similar survival to those not treatedby embolization. This study has emphasized that most of the reported benefits from immunotherapy are in patients with marker lung lesions and this therefore limits the number of patients available for this type of study.

In a prospective study of the humoral immune response to embolization and subsequent nephrectomy, Ritchie et al[16] reported on the use of monoclonal antibodies, in conjunction with flow cytometry, to enumerate circulating lymphocyte subsets with distinct functions in the regulation of the immune process. Analyses were perfurmed on 32 patients with histologically proven renal carcinoma at presentation and sequentially through their clinical course. It was found that untreated patients with advanced disease had a deficit of T cells with "helper/inducer" phenotype (Leu 3a+) and this resulted in abnormal T "helper/suppressor" (Leu 3a+/Leu 2a+) ratios.

Following nephrectomy, performed in 26 patients, there was a significant increase in the number of T cells with the "helper/inducer" phenotype and a significant increase in the T "H/S" ratios. Subsequent follow-up, at a minimum of two months (with the exception of six patients with evidence of disease progression) was then accompanied by a significant increase of the T-cell subset with the "suppressor/cytotoxic" phenotype (Leu 2a+).

Pre-operative renal arterial embolization resulted in an early transient lymphopenia. Subsequent response to embolization combined with nephrectomy was little different when compared with nephrectomy alone.

These findings, made possible by the vastly improved technology of cellular immunology, indicate that immune homeostasis is distorted by the presence of advanced tumor. Moreover the abnormalities can be reversed by removal of the tumor in patients with non-metastatic disease. Embolization however, was found to have little effect on these immunological parameters; a fact reflected by the clinical course of the patients so treated. Further analysis of functional aspects of the subsets involved should lead to more logical methods of immunological manipulation.

Other non-surgical treatments

Radiotherapy. Renal carcinomas have a radiosensitivity that is similar to glandular carcinomas but it is difficult to give this tumor a curative (6,000 rad) dose of radiotherapy because of the risk of radiation damage to adjacent normal tissue. The use

of smaller doses of radiotherapy (3 - 4,000 rad) pre-operatively was introduced mainly on the basis of anecdotal claims that radiation improved the operability of these masses[17]. Prospective studies have suggested that although the operability can sometimes be improved, there is no impact on survival[18].

The use of radiotherapy postoperatively has also been disappointing. In a retrospective study of the use of radiotherapy for any part of the management of this tumor there were no advantages and indeed it appeared that radiotherapy was consistently disadvantageous - but this was also an example of the danger of using retrospective data[19]. Prospective studies have shown no advantages for radiotherapy[20] and it must be concluded that radiotherapy has only a very limited role in the management of renal carcinoma, mainly in the palliation of metastatic foci especially bone lesions.

Hormone Therapy. The basis for the use of hormones in the management of renal carcinoma was the observation that these drugs inhibited the growth of estrogen-induced renal tumors in male Syrian golden hamsters[21,22]. Extrapolating from these laboratory observations, a variety of hormones have been used, mainly progester ones and androgens with most of the responses occurring with medroxyprogesterone (Provera). The reported response rates are variable. Bloom and Hendry[23] reported 55% subjective and 16.5% objective response rates in their own 80 patients; the objective response rate from a collected series of 588 patients was 11%. Attempts to improve these responses with other hormones or combinations of hormones and cytotoxic agents have not changed the objective response rate from about 10% [24]. Despite the generally disappointing experience with hormones such as medroxyprogesterone they remain the only drugs that can produce some subjective improvement and occasional objective responses.

Attempts to define the hormone receptor status of renal carcinomas have not been encouraging. Both androgen and progesterone receptors have been found but the levels are very low and their significance remains controversial. Concoline et al[25] have suggested that those with hormone receptors, especially progesterone receptors, are more responsive but in a prospective study of 89 cases Ronchi et al (1984) were unable to draw any conclusions on management from their receptor data.

Chemotherapy. Most drugs used as single agents have less than 20% and many cases less than 10% response rates. Vinblastine has the highest objective response rate (25%) but the range of responses (8-32%) reflects the limited value of this agent. Of the alkylating agents, cyclophosphamide and CCNU have shown some activity; of the antibiotics, bleomycin is more effective than adriamycin. The response rates with antimetabolites such as methotrexate and 5-fluorouracil are negligible and there have been no responses with cisplatin. Hydroxyurea and methyl GAG have some activity.

Combination chemotherapy with these agents has given slightly better response rates than might be expected but there is a considerable increase in toxicity and there is no good evidence of improved survival[24].

Immunotherapy. Reference has already been made to attempt to use an embolization effect as a form of active specific immunotherapy. Other forms of active specific immunotherapy have used a variety of tumor vaccines using either irradiated tumor cells, cell or membrane preparations or tumor extracts. Some encouraging results using polymerised cell membrane antigens and an adjuvant (tuberculin PPD) have been reported by Tykka. Active non-specific immunotherapy with Coley's toxin, BCG, C. Parvum and interferon have shown some anti-tumor activity.

Passive immunotherapy methods have attempted to transfer activitated cells or anti-sera without stimulation of the host response. Immune RNA produced no responses in one study but a 30% response rate in another study.

It is concluded that immunotherapy has produced some complete responses but these responses are almost all in patients with pulmonary metastases. There are few other responses except stable state. These treatments are associated with considerable toxicity and no prospective controlled data are yet available.

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DISCUSSION

Akdaş: I would like to present, very briefly, an interesting case. In 1981 a 60-yearold patient, was sent to me by one of my ENT colleagues. He had recently developed a paranasal sinus metastasis, the outcome of a kidney tumor, which had been removed in 1976. According to the histological investigation it was actually metastasis from hypernephroma. The other investigations were all normal. We just put him on hormonal treatment. After a year he developed brain metastasis and then we gave him radiotherapy, and he did well. Then he again developed bilateral sinus metastases. I think the recurrence was because they hadn't removed all the mass at the beginning; so he's still alive without any lung metastasis; I think its a very rare case.

Chisholm: Well of course the natural history is the problem, isn't it, in this disease?

Şimşek: I would like to ask two questions if I may. The first is for Professor Chisholm who drew a very pessimistic outline for therapy in cases of kidney tumors. What is the regimen you are giving to your patients right now?

Chisholm: This is Mr. Wickham's topic, so I will limit myself to saying that the primary treatment, the only treatment known in this world, at the moment, for renal carcinoma is a good nephrectomy; and the earlier you do it, and the smaller the tumor, the better the result. So don't misunderstand me, nephrectomy is the treatment for renal carcinoma. If you want to improve the surgical access with embolization that is perfectly acceptable; I mean I'm not saying that's bad. But don't do it if you think you're going to affect the immune status of the patient when there's no evidence. Once you've done the nephrectomy, and if you then have metastases you ask me what to do. Well, if you've got a solitary metastasis in a bone you'll do just exactly what you're always going to do, radiotherapy, and if you've got lung metastases, you're probably going to do just as I do with a great deal of reluctance; give them Provera®. And I don't do this, because I'm convinced of its usefulness, I do it in a way because in a small percentage of cases some improvement has been reported with it, and I know of no other chemotherapy. If you are in a special situation in an oncology unit you might wish to look at the Vincristine family of drugs. I think it looks as if those are the best, at the moment, but I would not suggest that that's routine; I would suggest that this is a matter for oncology unit investigation.

Şimşek: Thank you. I would like Doctor Besim to tell us about his experience of the toxic effects of embolization.

Besim: In our 10 cases we have only observed pain, no pyrexia.

Tellaloğlu: Some 20 years ago, we often came across reports in the journals stating that after nephrectomy for hypernephroma complete regression occurred in some cases. Is that still the nature of the tumor?

Chisholm: Well, I knew we could not avoid this subject, and I have slides of one, to me, convincing case of regression. This was a Hammersmith Hospital patient, in about 1970 to 1971, and the X-rays are, I think, persuasive. I think every one of us has one such case where we're forced to admit the lung metastases regressed. Whenever you talk about this, there's always the problem that, because very few people have ever biopsied these lung metastases, there is some doubt always if they really were metastases; but I think there are a number of convincing cases. I believe it; but it's rare. And in a way this is why we all do a nephrectomy even when we've got metastases because we remember a case that had regression of metastases so we go ahead again.

Khalifa: People tend to forget, or minimize the effect, of chemotherapy on patients. It makes them very miserable, and I think people should think twice before they send them home.

Chisholm: Well, I'm sure Professor Stuart would agree with this. I mean the sort of work that needs to be done should be done only in oncology units. I think it's quite wrong for these drugs to be used in a random way without proper control. I think it should be done in what people call "Center Referrals" because then the information will be documented and perhaps we'll get some results.

Hussien: As you say the sequence really is very gloomy. Do you think the sort of investigation which is being carried out like IVP, ultrasound, CT scan, and renogram is really necessary for the management of the patient?

Chisholm: I do not. It doesn't alter your management, but it does give you an idea of the prognosis.

Hussien: It doesn't affect the prognosis, though.

Chisholm: No, but I think it's nice to know where you're going with a patient. There's no doubt, the current views of most centers now who have CT, is that CT has replaced angiography. That's if you don't want to embolize the kidney. You're caught if you want to embolize the kidney, because then you've got to do an angiogram, but if you just want to define the extent of the tumor, in an ideal world, all you need is CT. It gives you the lung fields, the paraglands, and the involvement of the vena cava; in fact everything for the price of one test.