The need for routine adrenalectomy during surgical treatment for renal cell cancer: the Hannover experience

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Objectives To further clarify the need for routine adrenalectomy during the surgical treatment of renal cell cancer, as in the absence of clinically overt metastatic disease, tumorous lesions within the adrenal gland are found in only 2–10% of patients, with most being over-treated by adrenalectomy.

Patients and methods The medical records of 819 patients undergoing adrenalectomy combined with nephrectomy, irrespective of the local extension of the primary tumour or the clinical stage at first diagnosis, were reviewed to determine the reliability of currently available imaging methods in predicting adrenal gland metastases. Several patient and tumour characteristics were correlated with the presence of intra-adrenal metastases, and their possible independent prognostic value was determined by a multivariate logistic regression model.

Results There was metastatic spread into the adrenal gland in 27 of 819 (3.3%) patients. In only three of eight patients in whom the adrenal was identified as the only metastatic site were preoperative abdominal computed tomography scans interpreted as false-negative. On multivariate statistical analysis only the presence of distant metastases, vascular invasion within the primary tumour and multifocal growth of renal cell cancer within the tumour-bearing kidney were identified as independent predictors of the presence of intra-adrenal metastases.

Conclusions None of the patient or tumour characteristics evaluated reliably predicted the likelihood of adrenal metastases in patients with no evidence of disseminated metastatic spread. However, previously published data indicate that the frequency of metachronous metastases within the contralateral kidney (1.8–3.8%) is significantly higher than the risk of a preoperatively undetected isolated intra-adrenal metastatic lesion when currently available imaging modalities are applied. Therefore, routine adrenalectomy should not be recommended if the preoperative radiological examinations are normal.

Keywords renal cell cancer, adrenal metastases, adrenalectomy

Introduction

Since the initial recommendations made by Robson et al. [1] for the surgical treatment of RCC, adrenalectomy has become an integral part of radical nephrectomy. However, in the absence of clinically overt metastatic disease, tumorous lesions within the adrenal gland occur in 2–10% of patients [2,3], and thus most patients are over-treated by the routine removal of the adrenal gland. The increased morbidity in patients undergoing nephrectomy combined with adrenalectomy, including the extended operative duration and the possible development of hormonal disorders, has resulted in prolonged debate about the need for the routine removal of the ipsilateral adrenal gland as part of a perifascial nephrectomy for treating RCC [4].

Because there are now more refined imaging methods, e.g. abdominal ultrasonography, MRI and CT, that allow the diagnosis of renal tumours at an earlier stage, the risk of metastatic spread beyond the tumour-bearing kidneys has decreased. Whether intra-adrenal metastases can be diagnosed before surgery and with sufficient sensitivity remains in debate [5–13].

Based on the observation that at least some patients may have had therapeutic benefit from adrenalectomy when there were undetected adrenal metastases before surgery, adrenalectomy was recommended for all patients undergoing surgery for RCC [13]. In contrast, when leaving the adrenal gland untouched, nephron-preserving approaches were shown to give a similar prognosis to that of radical surgery [14–17]. Additionally, the relapse-free survival of patients with RCC undergoing nephrectomy combined with adrenalectomy equalled that after nephrectomy alone [4,12].
Moreover, despite radical surgery, the presence of adrenal metastases was associated with an uniformly poor outcome [4,12]. Thus the aim of the present study was to further clarify the need for routine adrenalectomy during surgery for RCC.

Patients and methods

The medical records of all patients undergoing radical nephrectomy between 1980 and 1995 at Hannover University Medical School were reviewed for preoperative radiological and histopathological findings during and after surgery, to determine the reliability of currently available imaging methods for predicting adrenal gland metastases. During this period all patients, irrespective of local tumour extension or the clinical stage at first diagnosis, were uniformly treated by nephrectomy with adrenalectomy. Several patient and tumour characteristics that were determined before surgery and during the pathological examination of the resected tumour-bearing kidney (e.g. patients' age, location of the tumour within the kidney, tumour size, tumour stage and the definite histological growth patterns; Table 1) [8,12,17] were correlated with the risk of developing adrenal metastases. Their possible independent prognostic value was determined by a multivariate logistic regression model. In the study period, 819 patients (328 female and 491 male) underwent nephroadrenalectomy for the treatment of RCC. The tumours were in the left and right kidney in 370 (45%) and 449 (55%), respectively. The preoperative tumour staging included CT of the abdomen and chest, and a bone scan. After surgical removal of the tumour-bearing kidney tumour invasion was classified as T1 (21 patients, 3%), T2 (418, 51%), T3 (343, 42%) and T4 (37, 4%) according to the TNM system [18].

The mean (range) tumour size was 70 (7–213) mm and they were histologically graded as G1 (129, 16%), G2 (460, 56%) and G3 (230, 28%). The growth pattern was classified according to the predominant pattern (solid, tubular, cystic and papillary). From the cell types identified, RCCs were characterized as clear-cell (86%), chromophilic, chromophobic, pleomorphic, eosinophilic and undifferentiated. Vascular invasion within the primary tumours was identified in 328 patients (40%). The upper pole of the tumour-bearing kidneys was affected in 409 (50%) patients.

At diagnosis, 215 (26%) patients had already developed regional lymph node or distant metastases. In addition to the lungs (79 patients, 10%) and bones (67, 8%), the most frequently affected metastatic sites were the ipsilateral hilar and the para-aortic lymph nodes (17%).

Fisher’s exact test was applied to assess the association of metastatic spread into the adrenal gland with other patient and tumour characteristics, e.g. histological grading, tumour stage, the location of RCC within the tumour-bearing kidney, the predominant growth pattern and cell type, and any vascular invasion within the primary tumour (Table 1). The possible independent prognostic value of these variables was evaluated in a multivariate logistic regression model.

Results

The adrenal gland was invaded by RCC in 16 of 409 patients, with RCC extending within the upper pole of the tumour-bearing kidney. In all of these patients

| Variable | P (Fisher's exact test) | P (logistic regression) |
|----------|------------------------|-------------------------|
| Before surgery | | |
| Age | 0.47 | 0.61 |
| Sex | 0.51 | 0.57 |
| Location of primary tumour (left vs right kidney) | 0.51 | 0.82 |
| Location of tumour within the kidney (on CT - upper pole vs mid vs lower pole) | 0.48 | 0.45 |
| Tumour size on CT | 0.62 | 0.53 |
| Presence of distant metastases | <0.01 | <0.01 |
| Resection kidney | | |
| Cell type: clear cell | 0.39 | 0.73 |
| chromophilic | 0.75 | 0.68 |
| eosinophilic | 0.53 | 0.55 |
| chromophobic | 0.71 | 0.81 |
| Growth pattern: solid | 0.39 | 0.71 |
| tubular | 0.21 | 0.48 |
| papillary | 0.40 | 0.92 |
| cystic | 0.45 | 0.51 |
| Location of tumour within kidney | 0.47 | 0.45 |
| Multifocal growth of 1\(^{st}\) tumour | <0.01 | <0.01 |
| Vascular invasion within 1\(^{st}\) tumour | <0.01 | <0.04 |
| Infiltration of renal capsule | <0.01 | 0.53 |
| Infiltration of perirenal fatty tissue | <0.01 | 0.32 |
| Invasion of renal pelvis | <0.01 | 0.14 |
| Hilar infiltration | <0.01 | 0.24 |
| Tumour stage (T1/2 vs T3/4) | <0.01 | 0.52 |
| Absolute tumour size | 0.62 | 0.30 |
| Tumour size (< 50 mm vs >50 mm) | 0.04 | 0.41 |
| Presence of regional lymph node metastases | <0.01 | 0.44 |
adrenal invasion was already diagnosed during the staging procedures before surgery (CT and ultrasonography). There was metastatic involvement of the adrenal gland in 27 patients (3.3%); in only eight of these patients (30%) was the adrenal gland identified as the only metastatic site. In the remaining 19 patients additional regional lymph node or distant metastases were found. CT before surgery gave false-negative results in five of these 19 patients and in three of the eight in whom the adrenal gland was identified as the only metastatic site. Therefore, adrenal metastases were detected during the staging examinations in 19 of 27 (70%) patients, as confirmed by the definitive histopathological examination of the resected gland.

Of the variables determined before surgery none were associated with a higher risk of metastatic spread into the ipsilateral adrenal gland (Table 1). However, the risk of adrenal metastases was associated with the presence of distant metastases ($P < 0.01$).

From the pathological examination of the resected kidney, tumour stage (T2 vs T3/T4: $P < 0.01$) and consequently the extension of the primary tumour within and beyond the renal capsule were associated with the presence of adrenal metastases. Only two patients with intra-adrenal metastatic lesions had a T2 tumour. In addition, invasion of the perirenal fatty tissue and the renal pelvis, and vascular invasion were associated with a significantly higher likelihood for tumorous involvement of the adrenal gland. The risk of adrenal metastases was also associated with the presence of regional lymph node metastases, multifocal tumour growth and tumour size (maximum diameter of the primary tumour $< 50$ vs $\geq 50$ mm). The mean tumour size was 68 mm and 90 mm in patients with or with no adrenal metastases, respectively. There were metastatic lesions within the adrenal gland in only three patients whose primary tumour was $< 50$ mm. The presence of adrenal metastases was not associated with the predominant growth pattern or the cell type within the primary tumour.

In multivariate analysis (logistic regression model) the presence of distant metastases, vascular invasion within the primary tumour and multifocal growth of RCC within the tumour-bearing kidney were identified as independent variables for predicting metastatic involvement of the adrenal gland (Table 1).

**Discussion**

Robson et al. [1] reported that combined nephron-adrenalectomy improved the clinical prognosis of patients with RCC compared with nephrectomy alone. Thus resection of the ipsilateral adrenal gland has become an integral part of surgery for renal tumours. Several factors have provoked the current discussion about the need for adrenalectomy in all patients. First, the increased detection of RCCs at an early tumour stage by ultrasonography and/or abdominal CT has reduced the risk of an inherent metastatic spread at first diagnosis. Second, new imaging methods have been devised that permit an exact diagnosis of intra-adrenal metastatic lesions before surgery, and will help to avoid the unnecessary removal of the adrenal gland [6,7,10,19].

The treatment of RCC by nephron-sparing surgery does not seem to increase the frequency of local tumour recurrences or decrease the long-term survival compared with the radical surgical approach [14,15,20]. The sensitivity of currently available imaging methods for reliably detecting metastatic lesions within the adrenal gland before surgery has been reported as 18–100% [6,7,10,13,19,21,22]. This variability might be a result of most previous investigations evaluating the clinical course of patients before the present generation of CT systems were available: in the present series the sensitivity of CT before surgery for detecting adrenal metastases was only 70%, the high rate of false-negative findings probably being a result of the same effect. However, clinical experience indicates that even currently available imaging methods cannot reliably detect metastatic lesions in all patients before surgery.

To improve the detection rate of adrenal metastases several authors have attempted to identify patient and tumour characteristics that predict the likelihood of metastatic spread into the adrenal gland, in addition to radiological approaches. Bülow et al. [8] reported that adrenal metastases only occurred in patients with pT3 RCC. Among 589 patients surgically treated for RCC, Knobloch et al. [13] found adrenal metastases in 0.9%, and in 6.6% of tumours classified as $\leq$T2 and $\geq$T3.

Tumour characteristics reportedly associated with a higher frequency of a tumorous involvement of the adrenal gland included vascular invasion within the primary tumour and the presence of regional lymph node metastases [18,21–24], multifocal tumour growth [24], pleomorphic cell type [24], anaplastic growth pattern [24] and advanced tumour size [8,12,13,23,24]. The predictive value of most of these variables for adrenal metastases in patients with RCC was confirmed in the present study.

Tsui et al. [25] determined the independent predictive value of criteria derived from the revised 1997 TNM staging system for the clinical prognosis of patients with RCC. Including 643 patients, the cancer-specific survival was clearly correlated with tumour stage, although the threshold size for localized T1 lesions was increased from 2.5 cm to 7 cm. Because the revised 1997 TNM criteria were correlated with survival on univariate analysis,
they were suggested as an appropriate adjustment in the staging of RCC. However, from the present results, the latest modification of the TNM system appears questionable, given the correlation between the risk of developing adrenal metastases and tumour size. Whereas in six patients with metastatic spread to the adrenal gland the tumour was 5–7 cm, in none of the tumours \( \leq 2.5 \text{ cm} \) and in three with a maximum diameter of 2.5–5 cm were adrenal metastases detected. This seems to indicate that although most patients classified as T1 by the revised 1997 TNM criteria have a more favourable clinical prognosis than those with T2 tumours in general, a subgroup of larger tumours currently classified as T1 have a more aggressive biological potential that was better reflected by the 1992 TNM criteria.

In contrast to the findings reported by Wunderlich et al. [24], there was no correlation with either cellular differentiation or dominant growth pattern of

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**Fig. 1.** Multislice CT scans before surgery in a 49-year-old man with bilateral renal masses: a, the large solid contrast-enhancing mass within the left kidney is in the lower parenchymal pole; b, on the right, a small contrast-enhancing solid renal lesion is visible in the dorsomedial parenchyma. Both renal masses are suspicious for RCC. c,d, In addition, nodular masses were detected within the adrenal glands bilaterally, indicating the presence of intra-adrenal metastases (diameter of the suspicious nodule within the left adrenal gland 1.5 cm).
the primary tumour with metastatic spread into the adrenal gland. In agreement with previous reports, the location of the RCC within the affected kidney had no predictive value for the presence of adrenal metastases.

The important question is whether routine adrenalectomy during surgery for RCC has any effect on recurrence-free and long-term survival. Comparing patients undergoing tumour nephrectomy with and without simultaneous adrenalectomy, Leibovich et al. [6] showed that routine adrenalectomy did not improve the clinical outcome of those patients. However, only a few studies have tried to determine the effect of adrenalectomy on the clinical course of the disease with manifest adrenal metastases. Whereas in one study [13] 32% of patients had no evident disease after a mean (range) follow-up of 42 (11–95) months, another [12] reported tumour progression in all patients with adrenal metastases. This led to the suggestion that adrenal involvement should constitute a stage category separate from the established TNM system. Kozak et al. [4] detected adrenal metastases in eight of 109 patients undergoing tumour nephroadrenalectomy. After a median (range) follow-up of 15 (4–63) months all these patients had died. Therefore, the clinical value of this surgical approach was as low as that for lymphadenectomy. Accordingly, in another series [23] that included 695 patients with RCC, only three of 30 (0.4% of the entire cohort) were continuously free of disease after 27 months. Results from an autopsy series [24] showed that 23 of 24 patients diagnosed with adrenal metastases had disseminated disease with distant or regional lymph node metastases. In contrast, in a simultaneously evaluated clinical series, further metastatic lesions in addition to adrenal metastases were found in only 30% of patients. In contrast to this last report, multiple metastatic lesions in addition to adrenal metastases were found in 19 of 27 patients in the present series. Therefore, the present findings further support those by Wunderlich et al. [24], that only very few patients have isolated metastases within the adrenal gland and that most of the remaining patients already have disseminated metastatic spread not detectable by currently available imaging methods at the time of first diagnosis. This would explain the poor clinical prognosis of patients with adrenal metastases even after successful adrenalectomy.

In the present series only eight of 819 patients (1%) presented with solitary adrenal metastases and in only three (0.4%) had the metastatic lesions within the adrenal gland not been detected before surgery. Irrespective of the apparently rare event of isolated metastatic spread to the adrenal gland, adrenal metastases can be diagnosed before surgery in most patients by current imaging methods (Fig. 1). As the present and previous studies agree (Table 2), several tumour characteristics, e.g. size and local extension of the primary tumour, are associated with a higher risk for developing adrenal metastases. In this context, the present study is the first to evaluate their independent prognostic importance within a multivariate statistical analysis. Because none of these variables has independent prognostic value, none can reliably predict the likelihood of adrenal metastases before surgery in patients with no evidence of disseminated metastatic spread. However, the frequency of metachronous metastases within the contralateral kidney is significantly higher (1.8–3.8%) [26] than the risk of an isolated adrenal metastasis. Therefore, if direct adrenal infiltration by large upper-pole tumours can be excluded, routine adrenalectomy should not be recommended if the radiological examinations before surgery show no abnormality.

**Table 2** The effect of adrenalectomy on the clinical prognosis of patients with RCC and recommendations for adrenalectomy combined with tumour nephrectomy, in current publications

| Ref. | No. of patients | Adrenal involvement | Effect on survival | Recommendation for routine adrenalectomy |
|------|-----------------|---------------------|--------------------|------------------------------------------|
| [2]  | 44              | NG                  | No                 | No                                       |
| [3]  | 138             | 8 (6)               | NG                 | Yes                                      |
| [8]  | 335             | 9 (2.6)             | NG                 | No (tumour stage T1/T2, normal CT)       |
| [23] | 299             | 11 (3.8)            | NG                 | No (macroscopically normal adrenals)     |
| [6]  | 225             | 3 (1.9)             | No                 | No                                       |
| [4]  | 225             | 8 (3.5)             | No                 | No                                       |
| [20] | 129             | 10 (7.8)            | NG                 | No (primary tumour < 5 cm)               |
| [12] | 162             | 3 (5.3)             | No                 | No (normal CT, macroscopically normal adrenals) |
| [10] | 77              | 7 (6.5)             | NG                 | No (normal CT)                           |
| [22] | 639             | 9 (1.4)             | NG                 | No (normal CT)                           |
| [13] | 589             | 19 (3.2)            | NG                 | Yes                                      |

NG, not given.

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