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Routine Bone Scan and Serum Alkaline Phosphatase for Staging in Patients with Renal Cell Carcinoma is Not Cost-effective

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In the Netherlands, a total of 1290 new cases of malignant renal tumours were reported in 1990 [1]. Of all renal tumours, 80–85% are renal cell carcinoma (RCC) and these account for 3% of all adult malignancies. Since 1930, the incidence and mortality of RCC have increased both for males and females. However, the rate of increase in mortality is less than the rate of increase in incidence [2]. Whether this is due to improved treatment for patients with RCC or due to wider application of screening methods, such as abdominal ultrasound, by which patients are selected in an earlier stage of RCC, is still unknown. The question of whether one should perform radical nephrectomy in patients with metastatic disease is still unanswered. According to some authors, nephrectomy improves survival in patients with metastatic RCC when some of the prognostic factors, such as solitary metastases (especially in the lung) or a low grade tumour are present [3,4]. Others revealed that nephrectomy increased survival only in those patients with bone metastases exclusively [5].

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These considerations make it clear that the optimal treatment choice depends very much on accurate pre-operative staging. Until recently, the standard staging procedure included ultrasound of the kidneys, CT scan of the abdomen and thorax, radionuclide bone scan and laboratory tests. To evaluate the results of a routine pre-operative bone scan and measurement of serum alkaline phosphatase (AP) in staging patients with RCC, 107 patients were evaluated from 1985 until 1993.

There were 61 males, median age 62 years (range 2–83) and 46 females, median age 63 years (range 18–81). 101 patients had a radical transabdominal tumour nephrectomy and a facultative regional lymph node dissection. Due to metastatic disease to lungs and bone, 6 patients did not undergo surgery. Pre-operative investigations included laboratory tests, ultrasound of the kidneys and CT scan of the abdomen and thorax. Urography was optional. AP was measured using the IFCC (International Federation of Clinical Chemistry) method with an AMP buffer at 37°C, reference value (13–120 U/l). In all 107 patients, a routine pre-operative bone scan with Tc-99m-MDP (Technetium Methylene Diphosphonate) 580 MBq was performed. Three to four hours after injection, whole body scans, and if considered necessary, detail images, were obtained. Hot spots on the bone scan were further evaluated by radiography of the affected sites.

Patients were followed from 24 until 144 months with a median of 70 months. Of the 107 patients with a pre-operative bone scan, 21 had suspicious lesions. 8 patients had a positive bone scan confirmed by osteolytic lesions seen on radiography. 13 patients had hot spots on the bone scan and were further evaluated by radiography of the affected sites. In all 13 patients, the lesions complied with degenerative abnormalities. 86 patients had a negative bone scan. Together with the 13 false positive scans, this accounts for a percentage of 92.5%.

When we divided patients into two groups of normal and elevated AP level, 71% has a normal AP and 29% has an elevated AP. In the group with a normal AP, values ranged between 39 U/l and 116 U/l, with a mean value of 81 U/l and a standard deviation of 17 U/l. In the patients with an elevated AP, values ranged between 123 U/l and 492 U/l, with a mean value of 227 U/l and a standard deviation 107 U/l. In 3 of the 8 patients with a positive bone scan, AP was elevated. However, in the patients with an elevated AP, only 10% had a positive bone scan. In the group of patients with normal AP levels, 6.5% had a positive bone scan (Figure 1).

From the patients with an elevated AP and a normal bone scan, 43% (12/28) had a normal AP level after nephrectomy within 6 months. These patients are still alive with no evidence of disease with a mean follow-up of 61 months. Another 21%

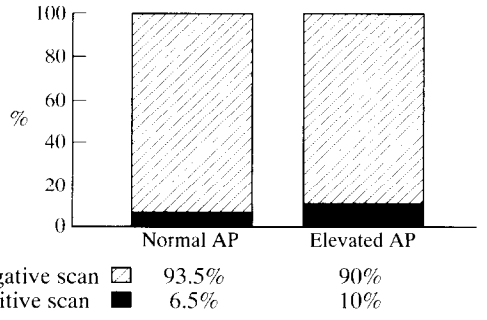

Figure 1. Results of bone scans in patients with normal (n=76) and elevated (n=31) alkaline phosphatase (AP) levels.

(6/28) of the patients with an elevated AP and normal bone scan developed soft tissue metastases within 9 months after nephrectomy and died subsequently. They had prolonged elevated AP levels until death.

In the group of patients with a positive bone scan (8), 5 complained of skeletal pain. The painful locations were confirmed on the bone scan. In the group of patients with a normal bone scan, there was no patient with complaints of skeletal pain as a presenting or associated symptom.

AP is a mixture of iso-enzymes which are mainly produced in the intestine, liver, placenta, kidney and bone. In bone, it is produced by osteoblasts and excreted in the bile. Elevated AP is present during pregnancy, in growing children and in patients with bone disease and hepatobiliary disease. AP as a prognostic marker for disease progression in RCC is controversial. An explanation for the high rate (90%) of patients with an elevated AP and normal bone scan might be the association of RCC with paraneoplastic syndromes. Few tumours are association with such a diversity of paraneoplastic syndromes as RCC, and the incidence of these systemic features in RCC patients is relatively high. Elevated AP was reported in 14.7% (64/434) of RCC patients and abnormal liver function tests (Bilirubin, SGOT, SGPT and SAP) in 15% (60/400) [5]. This syndrome of elevated liver function tests is associated with reversible non-metastatic hepatic dysfunction and is referred to as Staufer syndrome. The aetiology is unknown and, in the absence of hepatic metastases, these abnormal liver function tests revert to normal after nephrectomy. In the future, it may be helpful to determine the AP iso-enzymes to increase the sensitivity of AP, especially the bone specific fraction which is produced by osteoblasts. Another useful approach to determine whether an elevated AP level reflects hepatic or bone disease is to measure a related enzyme, 5-'nucleotidase, which is produced by hepatic canalicular microvilli but is not found in bone.

A routine pre-operative bone scan in RCC patients without skeletal pain is not indicated. In RCC patients, the chance of having bone metastases at presentation is small, even with an elevated AP, and these metastases are often symptomatic. AP is often elevated without evidence of (bone) metastases and can normalise after nephrectomy. The only indication for a bone scan in staging RCC patients is, therefore, skeletal pain.

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Thyroid Cancer: Different Outcomes to Chemotherapy According to Tumour Histology

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IN THE MANAGEMENT of thyroid carcinoma, doxorubicin alone, or in combination with cisplatin, is considered the most active regimen, although it gives unsatisfactory response rates with significant side-effects [1–3]. Epirubicin is endowed with a spectrum of activity similar to doxorubicin and an equivalent response rate with less cardiotoxicity and acute myelosuppression [4, 5]. Carboplatin produces less nephrotoxicity, neurotoxicity and vomiting than cisplatin [6, 7].

In an attempt to identify a well tolerated regimen which does not affect patients' quality of life, the association of epirubicin 75 mg/m^2 given by i.v. (intravenous) bolus on day 1, and carboplatin 100 mg/m^2 by 30 min infusion on days 1–3, repeated every 28 days, was proposed as first-line chemotherapy to patients aged $\leq$ 70 years, ECOG performance status $\leq$ 2, affected by histologically proven thyroid carcinoma (except medullary) not suitable for surgery or radioactive iodine. Eight cycles were planned except for the cases showing progressive disease. Response and toxicity were evaluated according to WHO-UICC criteria [8].

20 patients entered the study: all were suitable for the evaluation of response and toxicity. 10 patients were male and 10 female, the median age was 64 years (range 35–70), ECOG performance status was 0 in 8 patients and 1 in 12. Sites of disease were thyroid (8 patients), local relapse (7), regional nodes (12), distant nodes (3), lung (12) and bone (1). 12 patients were pretreated with locoregional surgery, 5 with radioactive iodine and 2 with radiotherapy. A total of 83 cycles of chemotherapy have been delivered, with a median of four cycles per patient (range 1–8). Treatment was well tolerated. No cases of grade 4 toxicity occurred; grade 3 anaemia occurred in 15% of patients, leucopenia was observed in 5% and nausea/vomiting in 5%. Alopecia was complete in 7 patients.

2 male patients achieved complete responses both lasting 12+ months: they were 70 years old with disease limited to the regional nodes, and in one case, local relapse. In these cases, the time to the best response was 5 and 3 months, respectively. One patient achieved a partial response lasting 4 months; 7 patients had stable disease for a median duration of 9 months (range

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