Increased Renal Retention of $^{99m}$Tc-Methylene Diphosphonate After Nephron-Sparing Surgery

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Nephron-sparing surgery has become established as an effective treatment for localized renal cell carcinoma when preservation of renal function is necessary. The surgery usually requires temporary renal artery occlusion and may induce ischemic renal damage. In this study, we retrospectively evaluated renal activity on bone scintigraphy after nephron-sparing surgery. Methods: Eleven patients who underwent nephron-sparing surgery for renal cell carcinoma and had a normal contralateral kidney were studied. A total of 12 bone scintigraphy images with $^{99m}$Tc-labeled methylene diphosphonate were obtained within 1 y after surgery in these patients to assess skeletal metastasis. Activity in the spared renal parenchyma was compared visually with that in the contralateral normal kidney. Results: The tumor was successfully resected in every patient, and no clinically significant complications occurred. Activity in the spared renal parenchyma was elevated in six of seven examinations performed within 21 d after surgery. In three examinations, the increase in renal activity was homogeneous, being relatively prominent near the surgical margin. Increased renal activity was not observed on five examinations performed 3 mo or more after surgery. Conclusion: Renal retention of bone-seeking agents is elevated in the early period after nephron-sparing surgery, probably as a result of ischemic insult during the surgical procedure. Bone scintigraphy may aid in evaluating the presence and degree of ischemic damage of the spared renal parenchyma.

Key Words: nephron-sparing surgery; $^{99m}$Tc-methylene diphosphonate; ischemia


Nephron-sparing surgery is a therapeutic method in which a portion of the involved kidney is resected and some renal parenchyma is spared. Although radical nephrectomy remains the standard therapy for localized renal cell carcinoma, nephron-sparing surgery is performed when there is a need to preserve as much total renal function as possible. Its utility is accepted in patients with a solitary kidney, bilateral tumors or a compromised contralateral kidney. Its indication is being extended to patients with small unilateral renal cell carcinoma and a normal contralateral kidney. The number of renal tumors incidentally detected by ultrasonography and CT has increased, and patients with incidental renal cell carcinoma appear to be candidates for nephron-sparing surgery. The role of this conservative procedure is presently evolving (1–3).

The common complications of nephron-sparing surgery include urinary fistula formation and acute renal failure (4). Temporary renal artery occlusion is usually required to reduce intraoperative bleeding but carries the risk of causing ischemic renal injury. The principal consideration in the utility of nephron-sparing surgery is to preserve renal function; therefore, great attention should be paid to minimizing ischemic renal damage.

$^{99m}$Tc-labeled phosphorus compounds are used for bone scintigraphy, and nonosseous accumulation is observed in various extraskeletal disorders (5,6). Bone-seeking agents are well known to be localized in tissues with ischemic damage, and adsorption with calcium deposits in the injured tissue is considered to play a major role (7,8). Animal experiments on the kidney have demonstrated that temporary occlusion of the renal artery induces elevation of the calcium concentration and increases the retention of $^{99m}$Tc-labeled phosphorus compounds in renal parenchyma (9,10). Increased renal activity has also been described in patients with renal ischemia (11–13). Ischemic injury during nephron-sparing surgery may elevate the retention of $^{99m}$Tc-labeled phosphorus compounds in the spared renal parenchyma.

We retrospectively reviewed bone scintigrams of patients who underwent nephron-sparing surgery before bone scintigraphy. The aim of this study was to determine whether renal retention of bone-seeking agents increases after nephron-sparing surgery.

MATERIALS AND METHODS

Patients

From January 1985 to February 1997, nephron-sparing surgery was performed in 23 patients with renal cell carcinoma. Bone scintigraphy was done routinely to assess skeletal metastasis but the timing was not specified. Twelve patients underwent bone scintigraphy within 1 y after surgery. One patient had a hypoplastastic kidney contralateral to the kidney with the tumor and was excluded from this study. Preoperative evaluation suggested a normal contralateral kidney in the remaining 11 patients, who became the
subjects of this study (8 men, 3 women; mean age 51.4 ± 6.4 y) (Table 1). Four patients had renal cell carcinoma in the right kidney and 7 in the left kidney. Tumor size ranged from 1.0 to 5.0 cm in maximum diameter. No patient received chemotherapy before bone scintigraphy.

Nephron-Sparing Surgery

Nephron-sparing surgery was defined in this study as a surgical procedure in which a renal lesion is resected with a margin of normal parenchyma.

The main renal vessels were occluded before resection of the tumor. In 10 patients, the kidney that was operated on was supplied by one main renal artery and the entire kidney became pale after occlusion. In the remaining patient (patient 11), blood was supplied through two renal arteries, one of which was occluded. The renal vein was not clamped in this patient. The duration of ischemia ranged from 12 to 70 min. In one patient (patient 1), the record of the length of ischemia was not available for review. The involved kidney was surface cooled with iced saline slush in all patients to prevent ischemic renal damage.

The tumor was resected with surrounding normal renal parenchyma that generally was 5 mm in thickness. After hemostasis was achieved, ligation of the main renal vessels was removed. Reflow was confirmed by the change in the superficial appearance of the kidney from pallor to redness.

Bone Scintigraphy

One patient underwent bone scintigraphy twice within 1 y after surgery; thus, a total of 12 examinations were reviewed. The interval between surgery and scintigraphy ranged from 5 to 304 d.

About 3 h after the intravenous administration of 740 MBq (20 mCi) 99mTc-labeled methylene diphosphonate (MDP), whole-body images and additional static views were obtained. A posterior abdominal spot image with the kidneys in the field of view was acquired, except in three examinations (examinations 4–6).

Activity in the renal parenchyma of the side operated on was compared visually with parenchymal activity in the contralateral kidney and was classified as strongly increased, mildly increased, equal or decreased. Heterogeneity in activity in the spared renal parenchyma was also assessed. It was considered positive only when obvious heterogeneity was present other than defects corresponding to the resection site or residual renal lesion. Visual interpretation was performed independently by two nuclear medicine physicians, and discrepancies were resolved by consensus between them. They were informed of the site of the resection and blinded as to the timing of bone scintigraphy after surgery.

RESULTS

In all patients, the renal tumor was successfully removed, and postoperative pathology confirmed renal cell carcinoma. Transient renal hypofunction was noted in 1 patient (patient 5) during the postoperative course. The patient’s serum creatinine level, which was 1.0 mg/dL before surgery, was elevated to 2.0 mg/dL soon after surgery and then recovered to 1.3 mg/dL at 1 wk after surgery. No other clinical complications were observed.

On the bone scintigrams, no abnormal deposits that would indicate metastatic osseous lesions were observed. Renal activity appeared to be normal on the contralateral side. In 6 of the 12 examinations, activity in the spared renal parenchyma was higher than in the contralateral kidney and equal in the remaining 6 examinations (Table 1). Activity was judged to be strongly increased in 2 examinations (Fig. 1) and mildly increased in 4. Homogeneity in renal activity was difficult to assess in 1 examination (examination 9) because of the presence of a large cyst in the involved kidney, so it was judged as negative. The elevated activity was obviously heterogeneous in 3 examinations. Activity was high throughout the spared renal parenchyma in these examinations and was relatively intense around the defect after resection (Fig. 2).

All examinations that indicated increased activity in the spared kidney were performed within 21 d after surgery. Of 7 examinations performed within 21 d after surgery, 6 showed increased renal activity on the side operated on (Table 2). In the patient in whom one of two renal arteries was occluded (patient 11), renal activity was not elevated, even in the ischemic parenchyma, on the bone scan acquired.

<table>
<thead>
<tr>
<th>Patient no.</th>
<th>Age (y)</th>
<th>Sex</th>
<th>Tumor size (cm)</th>
<th>Ischemia time (min)</th>
<th>Examination no.</th>
<th>POD</th>
<th>Renal activity</th>
<th>Heterogeneity</th>
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<td>27</td>
<td>12</td>
<td>9</td>
<td>←</td>
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POD = postoperative days; ← = equal; ↑ = mildly increased; ↑↑ = strongly increased.
9 d after surgery. Two examinations with strongly increased renal activity were performed 5 d and 6 d after surgery, and 4 with mildly increased activity from 13 to 21 d after surgery. Five examinations were performed at least 3 mo after surgery and did not show increased renal activity. One patient who underwent two bone scintographies exhibited mildly increased activity on the scan obtained 20 d after surgery and equal activity on the scan obtained 97 d after surgery.

Urinary retention in the collecting systems (an indication of urinary obstruction) was not noted. No bone scintigraphy suggested the presence of urinary fistula.

**DISCUSSION**

Diffuse increases in renal retention of bone-seeking agents have been observed in association with various conditions. These include urinary obstruction, ischemic renal damage, exposure to chemotherapeutic agents or other nephrotoxic drugs and previous radiation therapy (7–18). In this study, renal activity was increased in patients who had undergone nephron-sparing surgery and had not received chemotherapy. The increase was seen in the entire spared renal parenchyma and was not observed in the contralateral kidney. Urinary obstruction may occur after nephron-sparing surgery as the result of a blood clot or ureteral edema (4); however, active obstruction was not suggested on bone scintigraphy. These findings indicate that increased retention in the spared kidney was induced by ischemic renal injury during the surgery.

Temporary occlusion of the renal artery may induce ischemic renal damage, resulting in transient or permanent impairment of renal function (4, 19). In ischemic renal injury, excess calcium enters the cell and diffuses into the mitochondria (19). Elevated intracellular calcium concentrations may be related to increased retention of $^{99m}$Tc-labeled phosphorus compounds after nephron-sparing surgery. The ischemia is temporary in nephron-sparing surgery and reperfusion is confirmed during the surgical procedure. The reperfusion seems to contribute significantly to the increased retention of $^{99m}$Tc-labeled phosphorus compounds in the spared kidney, because it may cause damage by producing free radicals (19) in addition to ensuring the delivery of the intravenously

**TABLE 2**

<table>
<thead>
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<th>Interval</th>
<th>Increased renal activity</th>
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<tr>
<td></td>
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<tr>
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<td>6</td>
</tr>
<tr>
<td>More than 3 mo</td>
<td>0</td>
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</table>

*Interval = interval between surgery and bone scintigraphy.*
administered tracer. It has been reported that $^{99m}$Tc-labeled phosphorus compounds are highly retained in the rabbit kidney after temporary renal artery occlusion (9, 10), and this study indicated that such a phenomenon also occurs in the human kidney.

It has been reported that ischemic episodes of $<$30 min induce little damage, even at normothermia, and that ischemia up to 60 min can be well tolerated at hypothermia (19). In this study, increased activity was clearly observed, even in the kidney that suffered 12 min of ischemia at hypothermia. This finding indicates the possibility of occurrence of renal impairment after a short period of ischemia. Renal retention of $^{99m}$Tc-MDP may be a sensitive marker of ischemic renal damage.

Activity of bone-seeking agents was frequently increased when bone-seeking scintigraphy was performed within 21 d after nephron-sparing surgery. Strongly increased renal activity was demonstrated within 1 wk after surgery, and mild increase was shown from 1 wk to 3 wk after surgery. Renal activity was not elevated on bone scintigrams obtained 3 mo or more after surgery. Our observation suggests that increased renal retention appears soon after ischemic insult.

In 1 patient, two renal arteries were present and only one of them was occluded during the surgical procedure. The renal vein was not clamped to maintain an exit for blood supplied by the other artery. The bone scintigram of this patient, obtained 9 d postoperatively, did not show increased renal activity. Blood supply to one half of the kidney may have had a protective effect on the remaining half. However, the actual mechanism of protection is unclear because the renal artery is considered an end-artery system (1). Leaving the renal vein unclamped is reported to reduce ischemic damage (4), and our observation may be attributed to this finding.

The increase in renal activity was obviously heterogeneous on 3 examinations and was comparatively prominent near the defect caused by resection. Predominance in activity may suggest predominant impairment, and surgical manipulation other than global renal ischemia may have increased the damage to renal tissue around the surgical margin. Heterogeneity was not noted on all bone scintigrams that showed increased renal activity. The cause of heterogeneity was not clear in this retrospective study with a small population, and it remains to be clarified in future studies.

Preservation of renal function is essential in nephron-sparing surgery. To prevent ischemic injury, aggressive preoperative hydration (19) and intraoperative surface cooling (20–22) are often performed. Mannitol (23) and allopurinol (24) have been reported to protect the kidney from ischemic injury. A variety of techniques have been advocated to reduce ischemic damage during nephron-sparing surgery. Renal retention of $^{99m}$Tc-labeled phosphorus compounds may reflect the presence and degree of ischemic damage of the spared kidney and, consequently, may aid in evaluating the utility of methods to prevent ischemic renal damage. This study was conducted retrospectively and included a small number of patients. Additional investigation is needed to reveal the relationship between the degree of renal damage and renal activity.

**CONCLUSION**

Retention of $^{99m}$Tc-labeled phosphorus compounds in the spared renal parenchyma is elevated in the early period after nephron-sparing surgery. This finding seems to be attributable to ischemic renal damage during surgery and may contribute to the assessment of impairment in the spared kidney.

**REFERENCES**