Encouraging laparoscopic renal cryoablation outcomes at 3 years

In order to determine the oncological efficacy of laparoscopic renal cryoablation, meticulous long-term follow-up is necessary. Gill *et al*. have therefore investigated renal small tumors in 56 patients who underwent this minimally invasive procedure and had completed 3 years of follow-up.

After surgery, follow-up included radiological, histologic and renal function evaluation. In addition, MRI was performed at 1 day and at 1, 3, 6, 12, 18 and 24 months postoperatively, and then annually for a minimum of 3 years.

MRI results showed that the average cryolesion size decreased with time, averaging a 75% reduction at 3 years. Furthermore, 17 cryoblated tumors were undetectable on MRI scan at the end of the follow-up period. There was also minimal impact on renal function in these patients. A further 39 patients underwent 6-month postoperative CT-directed needle biopsy for histopathologic examination. This confirmed locally persistent/recurrent renal tumors in two patients. These patients underwent secondary laparoscopic radical nephrectomy, and at 2.5 and 3 years follow-up no evidence of locally/recurrent metastatic disease was found.

The authors believe that to achieve optimum results, renal cryoablation should be performed in carefully selected older patients with a small renal tumor (less than 3 cm). Even though these renal cryoablation outcomes are encouraging at 3 years and surgical complications minimal, the authors highlight the importance of a longer 5-year follow-up to renal cryoablation to validate the effectiveness of this minimally invasive approach.

Original article Gill IS *et al.* (2005) Renal cryoablation: outcome at 3 years. *J Urol* **173:** 1903–1907

CpG hypermethylation of the *GSTP1* promoter in prostate cancer patients from different ethnic groups

Glutathione S-transferase pi (GSTP1) has been the subject of several cancer studies. Recent work by Enokida and colleagues has investigated the role of inactivation of *GSTP1* by CpG hypermethylation in prostate cancer pathogenesis, and has asked whether this differs among ethnic groups.

Using a methylation-specific polymerase-chain-reaction technique, the team recorded the methylation status of the *GSTP1* promoter in 291 prostate cancer tissue samples. 170 samples were obtained from Asian patients, 44 from African-Americans, and 77 from Caucasians. The results were compared with those from 172 benign prostatic hyperplasia samples (96 from Asian patients, 38 from African-Americans, and 38 from Caucasians). As expected, this analysis showed that *GSTP1* hypermethylation was more common in prostate cancer than in benign prostatic hyperplasia (65.6% vs 24.5%, $P<0.0001$), across all ethnic groups. The difference was most pronounced among the African-American samples, however, and the authors suggest that *GSTP1* methylation is a useful biomarker for prostate cancer among this ethnic group.

Next, *GSTP1* methylation was correlated with pathologic stage and Gleason score. In both cases, the frequency of methylation was positively associated with the pathologic findings, suggesting a role for *GSTP1* methylation in tumor progression. Among the individual ethnic groups, however, this association was statistically significant only for the Asian patients.

In summary, the study indicates that *GSTP1* methylation is important in prostate cancer pathogenesis and that this epigenetic event differs among ethnic groups.

Original article Enokida H *et al.* (2005) Ethnic group-related differences in CpG hypermethylation of the GSTP1 gene promoter among African-American, Caucasian and Asian patients with prostate cancer. *Int J Cancer* **116:** 174–181

New salvage treatment for advanced urothelial tract cancers

Preclinical studies using xenograft models have shown that SCH66336 (lonafarnib), an orally administered tricyclic farnesyl transferase inhibitor, has significant antitumor activity. A European, multicenter study now demonstrates that combination therapy with SCH66336 and gemcitabine is a feasible second-line treatment in patients with advanced urothelial tract cancers, producing a higher overall response rate than is usually achieved in this setting.

Thirty-four patients were recruited to the study. All had previously received one line of chemotherapy for advanced transitional cell carcinoma of the bladder ($n=28$), renal pelvis ($n=4$) or ureter ($n=2$). With the exception of one patient who withdrew consent, patients received a median of three 28-day cycles of treatment, which consisted of continuous SCH66336 (150 mg each morning and 100 mg each evening, starting on day 2) and gemcitabine (1,000 mg/m^2 on days 1, 8 and 15).

The treatment was well tolerated in general. There were no cases of severe hematologic toxicity (grade 4 thrombocytopenia or febrile neutropenia), although grade 3 neutropenia and thrombocytopenia each occurred in six patients and grade 3 anemia was observed in nine patients. The most common non-hematologic grade 3 toxicities were fatigue (eight patients), diarrhea (four patients), and nausea/vomiting (three patients).

Of 31 evaluable patients, one achieved a complete response and nine achieved a partial response. The corresponding overall response rate of 32.3% (95% CI 17–51%) was higher than in most published studies in this setting. An analysis in 11 of the patients showed that SCH66336 did not affect the pharmacokinetics of gemcitabine.

The investigators recommend that the observed activity of this drug combination should now be assessed in randomized trials.

Original article Theodore C *et al.* (2005) Multicentre EORTC study 16997: feasibility and phase II trial of farnesyl transferase inhibitor & gemcitabine combination in salvage treatment of advanced urothelial tract cancers. *Eur J Cancer* **41:** 1150–1157

Does participation in a trial affect clinical outcome?

A systematic review published in the *British Medical Journal* has asked whether participation in randomized controlled trials (RCTs) influences clinical outcomes. By comparing outcomes of RCT participants with those of individuals receiving similar treatments outside of trials, the researchers demonstrated that RCTs were associated with neither a harmful nor a beneficial effect.

There has been some debate over whether participation in a randomized trial increases a patient's risk of a bad outcome, and whether the benefit of such studies is restricted to future patients. Furthermore, the applicability of clinical trial results to normal clinical practice has been questioned. Several studies have been undertaken to address these questions, but no single study has provided conclusive evidence. Vist *et al.* carried out a systematic review of 50 non-randomized cohort studies, and five clinical trials in which patients were randomized to participation or the option of participation. The studies were in the fields of oncology, obstetrics and gynecology, cardiology or other internal medicine, psychology and drug misuse, pediatrics, and respiration. The studies included data on a total of 31,140 RCT participants and 20,380 comparable non-participants who received similar treatment.

Of 73 dichotomous main outcomes studied, the majority (63) showed no statistically significant difference between RCT participants and non-participants, whereas eight showed significantly better outcomes and two showed significantly worse outcomes for RCT participants. The pooled results for 18 continuous outcomes showed no statistically significant difference between those treated inside or outside of RCTs.

In summary, this systematic review indicates that participation in RCTs is associated with neither benefit or harm, compared with the use of similar interventions outside trials. These findings support the idea that the results of RCTs are generally applicable to clinical practice.

Original article Vist GE *et al.* (2005) Systematic review to determine whether participation in a trial influences outcome. *BMJ* **330:** 1175