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Selected reports edited by Janet Fricker

Complications from robotic prostatectomy no better than conventional surgery

→ Journal of Clinical Oncology

Problems with continence and sexual function are common following both robot-assisted laparoscopic radical prostatectomy (RALRP) and open retropubic radical prostatectomy (ORRP), a US study has found.

Conventional wisdom holds that men undergoing the robotic procedure experience less post-surgical urinary incontinence and erectile dysfunction compared to those undergoing the traditional surgical approach. In the current study Michael Barry and colleagues, from Massachusetts General Hospital, Boston, compared the continence and sexual function of Medicare enrolees following treatment with either ORRP or RALRP. Investigators used a population-based random sample drawn from 20% of Medicare prostatectomy claims filed between August and December 2008. At a median of 14 months following surgery, participants were asked to complete a mailed survey that included self-ratings of problems with urinary continence and sexual function.

Completed surveys were obtained from 685 participants, with 406 reporting having undergone RALRP and 220 ORRP. When results were "dichotomized" 27.1% of men who had undergone ORRP reported a moderate or big problem with continence compared with 33.3% who had undergone RALRP (P=0.113). For sexual function, 89% of men who underwent ORRP reported a moderate or big problem compared with 87.5% who had undergone RALRP (P=0.57).

"Our findings demonstrate the risks patients actually face with these two procedures in the contemporary national surgical experience in Medicare. Low case volumes likely contribute to the high risk of adverse effects with both procedures in the general population," write the authors. Whether the risk of adverse effects will be lower over time with RALRP, they add, remains to be seen, but in the interim, there is a question about value for money.

"The apparent lack of better outcomes associated with RALRP also calls into question whether Medicare should pay more for this procedure until prospective large-scale outcome studies from the typical sites performing these procedures demonstrate better results in terms of adverse effects and cancer control," they conclude.

In an accompanying commentary, Matthew Cooperberg and colleagues, from the University of California, San Francisco, write, "Although methodologically much more sound than an earlier analysis that tried to determine health-related quality-of-life outcomes on the basis of claims data alone, the study… still has significant limitations."

These limitation, the say, include the fact that all the subjects were aged 65 or older, which means there are no data to show whether results might have differed in younger patients. As baseline function was not measured, it is not possible to say whether these were the same for the two study groups. Furthermore, the survey instrument assessed only "bother" and not function. They also point out that all the operations were performed in 2008, when many surgeons may have still been "learning" the robot-assisted technique.

"Although the exact learning curve for robot-assisted surgery remains unclear, it has been estimated that high proficiency in this technique may require that more than 200 surgeries be performed," they write.

■ MJ Barry, PM Gallagher et al. Adverse effects of robotic-assisted laparoscopic versus open retropubic radical prostatectomy among a nationwide random sample of Medicare-age men. *JCO* 10 February 2012, 30:513–518

■ MR Cooperberg, AY Odisho and PR Carroll. Outcomes for radical prostatectomy: is it the singer, the song, or both? *ibid*, pp 476–478

Semuloparin reduces thromboembolic events during chemotherapy

→ New England Journal of Medicine

Semuloparin – the ultra-low molecular weight heparin – reduces the incidence of thromboembolic events in cancer patients undergoing chemotherapy, the SAVE-ONCO study has concluded.

It is well known that cancer patients receiving chemotherapy are at increased risk of venous thromboembolism, with complications including otherwise unnecessary hospitalisations, interruptions of chemotherapy and anticoagulant treatments or insertions of a vena cava filter. Current guidelines recommend antithrombotic prophylaxis for patients with cancer admitted to hospital for medical illness (administered for the duration of their hospital stay) and for patients undergoing surgery for cancer, but not for routine use in ambulatory chemotherapy patients.

In the double-blind multicentre trial, Giancarlo Agnelli, from the University of Perugia, Italy, and international colleagues, randomised 3212 patients with a wide range of metastatic or locally advanced solid tumours to receive subcutaneous semuloparin 20 mg once daily, or placebo, until there was a change of chemotherapy. Patients in the study, who had just commenced a number of different chemotherapy regimens, were recruited from 395 centres in 47 countries.

Results show that, at a median treatment duration of 3.5 months, venous thromboembolism occurred in 1.2% of patients receiving semuloparin, compared with 3.4% receiving placebo (HR 0.36, 95%CI 0.21–0.60; $P<0.001$). The incidence of clinically relevant bleeding was 2.8% in the semuloparin group versus 2.0% in the placebo group (HR 1.40, 95%CI 0.89–2.21), with major bleeding occurring in 1.2% receiving semuloparin versus 1.1 % receiving placebo (HR 1.05, 95%CI 0.55–1.99). The incidence of other adverse events was similar in the two treatment arms.

"The results of this study show that thromboprophylaxis with the ultra-low-molecular-weight heparin semuloparin, as compared with placebo, reduces the risk of venous thromboembolism among patients receiving chemotherapy for cancer, with no apparent increase in the incidence of major bleeding," conclude the authors.

Several criteria have been proposed to identify cancer patients at high risk for venous thromboembolism, they add, including specific cancer types, chemotherapy regimens, levels of serum tissue-factor microparticles or P-selectin and predictive scores for chemotherapy-related thrombosis. They suggest that stratification for the risk of venous thromboembolism among patients with cancer might be clinically useful.

In the accompanying commentary, Elie Akl and Holger Schünemann, from the State University of New York, undertake a new pooled analysis of low molecular weight heparin use in cancer patients including data from their earlier Cochrane review of nine trials, the SAVE-ONCO trial and a recent third study including 503 patients. When these studies are combined, the relative risk for symptomatic venous thromboembolism is 0.57 and for death 0.94.

"The key questions that are not answered conclusively relate to the effect of treatment with low-molecular-weight heparin on quality of life and whether such treatment affects tumor growth or dissemination," write the authors. At time of publication, they add, at least six additional low molecular weight heparin trials in cancer patients, aiming to enrol around 3500 patients in total, are ongoing.

■ G Agnelli, D George, A Kakkar et al. Semuloparin for thromboprophylaxis in patients receiving chemotherapy for cancer. *NEJM* 16 February 2012, 366:501–509

■ E Akl and H Schünemann. Routine heparin for patients with cancer? One answer, more questions. *ibid*, pp 661–662

BRCA1/2 mutations predict ovarian cancer survival

➜ JAMA

Among women with invasive epithelial ovarian cancer, mutations in the BRCA1 or BRCA2 genes are associated with improved five-year survival in comparison to women who do not carry the mutations. The UK study revealing that BRCA2 carriers show the best prognosis represents the largest BRCA-associated ovarian cancer outcomes study reported to date.

Approximately 10% of women with invasive epithelial ovarian cancer carry deleterious germline mutations in BRCA1 or BRCA2. The goal of the study by Paul Pharoah and colleagues, from the University of Cambridge, UK, was to gain a better understanding of the effect on survival of BRCA1/2 mutations compared to wild-type BRCA1/2 from a multiple case series of epithelial ovarian cancer.

In the pooled analysis, participants were drawn from 26 international studies that had enrolled participants between 1987 and 2010 (10 studies from the US, six from Europe, two from Israel, one from Hong Kong, one from Canada, one from Australia and five from the UK). Altogether data were obtained from 3879 women with ovarian cancer – 909 with pathogenic germline mutations in BRCA1, 304 with germline mutations in BRCA2 and 2666 who did not carry BRCA1 or BRCA2 mutations.

Results show that the five-year overall survival was 36% (95%CI 34%–38%) for non-carriers, 44% (95% CI 40%–48%) for BRCA1 carriers, and 52% (95%CI 46%–58%) for BRCA2 carriers.

The study also showed that the clinical characteristics of epithelial ovarian cancer among BRCA1/2 carriers differed from that of non-carriers. Tumours with serous histology, high grade and advanced stage were all more likely among carriers of both mutations.

In a secondary analysis, the investigators found that the survival advantage conferred by BRCA1 mutations was partially mitigated as the mutation site moved from the 5' to 3' end. This suggests, they write, that the site of the BRCA1 mutation may be of individual prognostic importance.

"*BRCA1* and *BRCA2* carriers with EOC [epithelial ovarian cancer] respond better than non carriers to platinum-based chemotherapies and have improved survival despite the fact that the disease is generally diagnosed at a later stage and higher grade," write the authors. The findings, they add, could be used by healthcare professionals for patient counselling regarding expected survival.

"Given the important prognostic information provided by *BRCA1* and *BRCA2* status and the potential for personalized treatment in carriers, the routine testing of women presenting with high grade serous EOC may now be warranted," they write.

In an accompanying commentary, David Hyman and David Spriggs, from Memorial Sloan-Kettering Cancer Center, New York, write that the findings represent the latest evidence that ovarian cancer is a much more genetically and biologically heterogeneous disease than previously appreciated. "Further studies in similarly large data sets are needed to better understand the effects of somatic and epigenetic alterations in *BRCA* gene function as well as

complex interactions with other inherited alleles. The accelerating availability of detailed somatic and germline genetic information will challenge all physicians who stand at the bedside of patients with cancer and struggle to deliver compassionate, individualized care."

■ K Bolton, G Chenevix-Trench, C Goh et al. Association between *BRCA1* and *BRCA2* mutations and survival in women with invasive epithelial ovarian cancer. *JAMA*. 25 January 2012, 307:382–390

■ D Hyman, D Spriggs. Unwrapping the implications of *BRCA1* and *BRCA2* in ovarian cancer. *ibid*, pp 408–409

Adjuvant chemotherapy improves outcomes following D2 gastrectomy

→ The Lancet

Adjuvant chemotherapy should be considered as a treatment option after curative D2 gastrectomy, the phase 3 CLASSIC study has concluded.

In Eastern Asian countries (especially Japan and Korea) D2 lymph node dissection (defined as dissection of group 1 and 2 lymph nodes) is regularly performed as a standard procedure for gastric cancer over D1 lymph node dissection (dissection of group 1 lymph nodes only). In western countries, D2 dissection has been associated with higher morbidity and mortality, although recent studies demonstrate that western surgeons can be trained to perform D2 gastrectomy for selected patients with low morbidity and mortality.

With guidelines now advocating D2 dissection in centres with specialist expertise, increased acceptance of D2 gastrectomy raises questions about the optimum adjuvant therapy for patients with operable gastric cancer. The Capecitabine and Oxaliplatin Adjuvant Study in Stomach Cancer (CLASSIC) study, was designed to compare the effect of adjuvant capecitabine plus oxaliplatin after D2 gastrectomy with surgery alone on disease-free survival in patients with stage II or III gastric cancer.

In the study, led by Yung-Jue Bang from Seoul National University College of Medicine, in Jongno-gu, Seoul, 1035 patients with stage II or III gastric cancer were randomly assigned in a 1:1 ratio to adjuvant chemotherapy (n=520) or surgery alone (n=515). The study was undertaken in 37 centres in South Korea, China and Taiwan.

Results show that the three-year disease-free survival was 74% in the chemotherapy and surgery group versus 69% in the surgery alone group (HR 0.56, 95%CI 0.44–0.72; P<0.0001). Grade 3 or 4 adverse events were reported in 56% of patients in the chemotherapy and surgery group versus 6% in the surgery only group.

"This study shows that a 6 month course of chemotherapy after D2 gastrectomy improves 3-year disease-free survival compared with surgery only," conclude the authors.

Although overall survival data from the CLASSIC trial are not yet mature, the results suggest an improvement with chemotherapy compared with surgery alone. "An analysis after a median follow-up of 5 years is planned to conclusively establish the overall survival benefit of capecitabine and oxaliplatin in this setting," write the authors. A key question for the trial, (as with any trial undertaken in one geographical region), they add, is whether findings can be generalised to other regions where disease management practices might differ.

In an accompanying commentary, Toshirou Nishida, from Osaka Police Hospital, Japan, raises the issue of adherence and safety. With more than half of patients in the CLASSIC study who were treated with chemotherapy experiencing grade 3 or 4 adverse events, nearly 10% withdrawing due to adverse events and 20% refusing treatment, he writes, non-adherence could be considered a risk of compromising disease outcomes.

"Identification of higher-risk patients and prediction of drug efficacy by biomarkers, and introduction of targeted agents such as trastuzumab, should be considered for adjuvant therapy of gastric cancer in the future," writes Nishida.

■ Y Bang, Y Kim, H Yang et al. Adjuvant capecitabine and oxaliplatin for gastric cancer after D2 gastrectomy (CLASSIC): a phase 3 open-label, randomised controlled trial. *Lancet* 28 January 2012, 379:315–321

■ T Nishida. Adjuvant therapy for gastric cancer after D2 gastrectomy. *ibid*, pp 291–292

Everolimus overcomes resistance to hormone therapy

→ New England Journal of Medicine

Everolimus combined with the aromatase inhibitor exemestane extended progression-free survival in postmenopausal women with advanced hormone-receptor-positive breast cancer, the BOLERO-2 study has found. The international phase III study, first published online to coincide with presentation at the 2011 San Antonio Breast Cancer Symposium, showed that combination treatment more than doubled progression-free survival compared to exemestane alone.

Resistance to endocrine therapy in breast cancer has been associated with activation of the mammalian target of rapamycin (mTOR) intracellular signalling pathway. Everolimus, an immunosuppressant agent used to prevent organ transplant rejection, is known to inhibit the mTOR protein. In preclinical studies, everolimus in combination with aromatase inhibitors resulted in both the synergistic inhibition of proliferation and the induction of apoptosis.

In the Breast Cancer Trials of Oral Everolimus-2 (BOLERO-2) study, José Baselga, from Massachusetts General Hospital Cancer Center, Boston, and international colleagues, randomly assigned 724 women with hormone-receptor-positive advanced breast cancer to receive either the combination of everolimus and exemestane (n=485; combination-therapy group) or exemestane and placebo (n=239; exemestane only group). The patients, who were recruited from 189 centres in 24 countries, had experienced either recurrence or disease

progression while receiving previous therapy with a nonsteroidal aromatase inhibitor (anastrozole or letrozole) in the adjuvant setting or to treat advanced disease.

At interim analysis the median progression-free survival was 6.9 months in the combination therapy group versus 2.8 months in the exemestane-alone group (HR 0.43, 95%CI 0.35–0.54; $P<0.001$). According to central assessment, the median progression-free survival was 10.6 months in the combination therapy group versus 4.1 months in the exemestane-alone group (HR 0.36, 95%CI 0.27–0.47; $P<0.001$).

Serious adverse events were reported by 23% of patients in the combination therapy group versus 11% in the exemestane-alone group. Stomatitis was the most common grade 3 or 4 adverse event, occurring in 8% of patients in the combination group versus 1% in the exemestane-alone group. This was followed by anaemia (6% vs >1%), dyspnoea (4% vs 1%) and hyperglycaemia (4% vs >1%).

The positive results in the study, write the authors, are consistent with the outcomes of two earlier studies of everolimus and anti-oestrogen therapy in hormone-receptor-positive breast cancer patients. In one study, neoadjuvant everolimus combined with letrozole improved the clinical response rate and decreased tumour cell proliferation in patients with newly diagnosed breast cancer; while in a second study the combination of everolimus and tamoxifen increased progression-free survival in women with oestrogen-positive advanced breast cancer previously treated with an aromatase inhibitor.

"Taken together, these studies suggest that everolimus adds to the anticancer activity of antiestrogen therapy in a variety of clinical settings and with different classes of endocrine agents," write the authors.

But benefits should be weighed against the side-effects observed with everolimus, they add. "The potential of everolimus to benefit patient survival is not yet known," they caution.

■ J Baselga, M Campone, M Piccart et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. *NEJM* 9 February 2012, 366:520–529

Adjuvant chemotherapy adds no benefit over chemoradiation alone in nasopharyngeal cancer

➜ Lancet Oncology

Adding adjuvant cisplatin and fluorouracil chemotherapy to concurrent chemoradiotherapy in patients with nasopharyngeal carcinoma confers no survival benefit, reports a Chinese study.

In recent years, seven randomised phase III studies comparing chemoradiation with radiotherapy alone have confirmed the value of chemotherapy on survival for advanced nasopharyngeal carcinoma. However, with three of these trials adding concurrent chemotherapy to radiotherapy only and four using the regimen of concurrent chemoradiotherapy plus adjuvant chemotherapy, investigators have been "unclear" as to whether adjuvant chemotherapy might deliver additional survival benefits over concurrent chemoradiotherapy.

In the current study, Jun Ma and colleagues, from Sun Yat-Sen University Cancer Centre, Guangzhou, China, set out to investigate whether addition of adjuvant chemotherapy to concurrent chemoradiotherapy delivered further benefits. Between June 2006 and March 2010, 508 patients with non-metastatic stage III or IV nasopharyngeal carcinoma were randomised to receive concurrent chemoradiotherapy plus adjuvant chemotherapy (n=251) or concurrent chemoradiotherapy alone (n=257).

Patients in both groups received 40 mg/m² cisplatin weekly for up to seven weeks, given concurrently with radiotherapy at 2.0–2.27 Gy per fraction, with five daily fractions per week for six to seven weeks. In addition, the chemotherapy adjuvant group received 80 mg/m² adjuvant cisplatin and 800 mg/m² per day fluorouracil for 120 h every four weeks for three cycles. The study was conducted in seven institutions in China.

At a median follow-up of 37.8 months, the estimated two-year failure-free survival was 86% in the chemoradiotherapy plus adjuvant chemotherapy group, versus 84% in the chemoradiotherapy only group (P=0.13). Adverse events were similar in both groups, with the most common being stomatitis, which occurred in 31% of patients receiving chemoradiotherapy plus adjuvant treatment and 32% receiving chemoradiotherapy alone.

"In our trial, adjuvant cisplatin and fluorouracil chemotherapy did not improve outcome, with no significant effect on the risk of treatment failure, or estimated 2 year failure-free survival, overall survival, distant failure-free survival, or locoregional failure-free survival," write the authors.

One possibility, they add, is that adjuvant cisplatin and fluorouracil does not represent an effective combination for eradication of micrometastases in nasopharyngeal carcinoma. "New combinations of more tolerable drugs that might improve efficacy of chemotherapy as an adjunct in advanced nasopharyngeal chemotherapy should be investigated," they write.

In an accompanying commentary, Joseph Wee, from Duke-NUS Graduate Medical School, Singapore, writes that two recent reports suggest that chemoradiation with first-generation drugs appears to work only in patients with earlier stage disease with lower distant tumour burden.

This raises the question, he adds, of whether the addition of a third or fourth agent might make a difference to outcomes. "This strategy is being investigated by several groups in the phase 3 setting, and are being done in the neoadjuvant setting to overcome the poor compliance if chemotherapy is given after radiotherapy," he writes.

■ L Chen, C Hu, X Zhong et al. Concurrent chemoradiotherapy plus adjuvant chemotherapy versus concurrent chemoradiotherapy alone in patients with locoregionally advanced nasopharyngeal carcinoma: a phase 3 multicentre randomised controlled trial. *Lancet Oncol* February 2012, 13:163–171

■ J Wee. Nasopharyngeal cancer: a promising future. *ibid*, pp 116–117