

21st century. The studies will focus on post-secondary education, with an emphasis on medicine, public health, and nursing, in all regions of the world, encompassing both instructional and institutional aspects of educational systems as they interact with health systems. The Commission expects to organise consultations in Africa, Asia, and Latin America in mid-2010. Its final report will be submitted to *The Lancet* for publication in November, 2010. Findings and recommendations will form the basis of enlightened advocacy to accelerate the transformation of professional education for health in the 21st century.

The Commission is surveying schools of medicine, nursing, and public health. Readers are encouraged to respond to this survey available on the Commission's website.¹

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Lymphadenectomy in endometrial cancer: when, not if

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The lack of consensus for primary surgical treatment of endometrial cancer, the most common gynaecological cancer, is deplorable. Whether lymphadenectomy should be done together with hysterectomy has been debated at length and passionately. Resolution of this problem has been confounded by several issues, such as selection of patients, the perceived goals of lymphadenectomy, and clinicians' failure to recognise the known routes of lymphatic spread from the uterus.¹ In practice, lymphadenectomy varies from complete omission, to various iterations of lymph-node sampling, to systematic lymphadenectomy. Furthermore, the extent of lymphadenectomy ranges from pelvic-node dissection alone to dissection of the para-aortic area, which can include the aortic bifurcation to the inferior mesenteric artery and up to the renal vessels.

Although the emergence of laparoscopic surgery has resulted in important improvements in short-term morbidity, this approach, even in the best of hands, could restrict the extent of para-aortic lymphadenectomy to the inferior mesenteric artery, an anatomical boundary

with no importance in gynaecology other than convenience.² This practice pattern has developed despite the fact that 77% of patients with para-aortic metastases harbour disease above the inferior mesenteric artery.³ In view of the strong association between obesity and endometrial cancer, the indications for and extent of lymphadenectomy are frequently determined more by body habitus than by objective pathological findings or formal risk assessments.

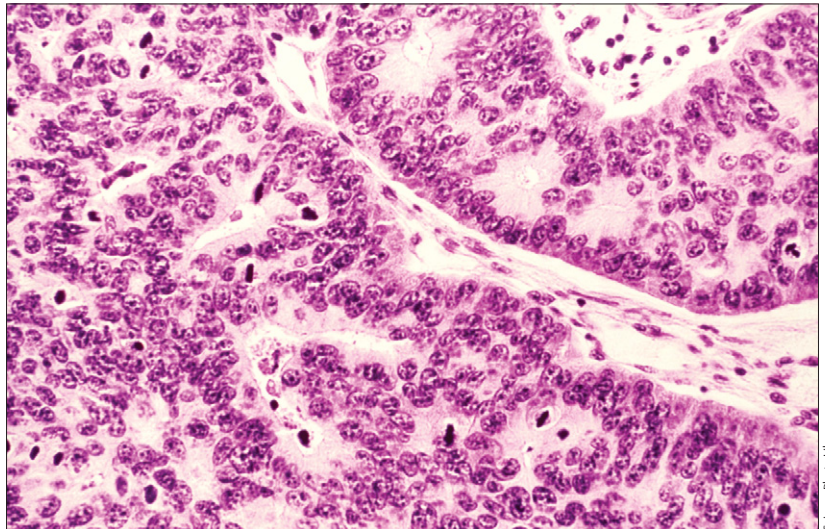
The challenges outlined above were evident in two randomised trials investigating the benefits of pelvic lymphadenectomy for endometrial cancer.^{4,5} Although neither trial showed differences in outcome between patients who did and did not undergo lymphadenectomy, both studies had serious deficiencies.^{6,7} Perhaps most importantly, both investigations were done in patients with a risk of lymphatic involvement of only 9–13%. Lymphadenectomy is unlikely to be beneficial unless the cohort studied has substantial risk of lymphatic disease. We have shown that histological subtype, tumour size, tumour grade, and myometrial

invasion can be used to identify patients with a negligible risk of lymphatic spread.^{8,9} About 27% of patients referred to our institution with endometrial cancer meet these criteria, and lymphadenectomy is omitted altogether. However, the remaining patients undergo a systematic pelvic and para-aortic lymphadenectomy to direct postoperative treatment.

In *The Lancet* today, Yukiharu Todo and colleagues report results from their comparative cohort study (SEPAL),¹⁰ in which they avoided most of the pitfalls that have plagued previous investigations of lymphadenectomy. Although retrospective, by comparison of two practice standards that differed mainly in the use of para-aortic lymphadenectomy, bias was kept to a minimum. The authors report that the addition of para-aortic lymphadenectomy to hysterectomy and pelvic lymphadenectomy reduced the risk of death, with a hazard ratio of 0.44 (95% CI 0.30–0.64, $p < 0.0001$).

Despite some degree of confounding with postoperative treatment, multivariate analyses showed that use of para-aortic lymphadenectomy and adjuvant chemotherapy were significantly and independently associated with survival of patients at intermediate and high risk of recurrence. The authors report excellent lymph-node counts, and the para-aortic dissection was systematic and extended to the renal vessels routinely. The fact that para-aortic lymphadenectomy was only beneficial to the group of patients at highest risk of harbouring lymphatic metastases is not surprising. 16% of the entire cohort was shown to have metastatic nodes, but 27% of those at intermediate or high risk, the cohort benefiting from para-aortic dissection, had positive lymph nodes.

A well-designed retrospective investigation can be more informative than a poorly designed prospective randomised trial, but Todo and colleagues correctly conclude that their results must be validated by a randomised study. We believe that a randomised trial should include four elements. First, the study should focus on patients at high risk of recurrence only. Second, treatment of patients assigned to receive no lymphadenectomy should be according to present standards for patients who have not had their stage of cancer assessed. Third, the status of lymph nodes should be used to direct postoperative treatment for patients assigned to receive lymphadenectomy. If nodal status is not taken into account, lymphadenectomy might add morbidity



Uterine adenocarcinoma

Surface epithelial cells of endometrium are stained pink and forming cavities (white); adenocarcinoma cells are long, irregularly shaped with large nuclei.

without accompanying improvements in outcome. Last, patients assigned to lymphadenectomy should receive a systematic pelvic and para-aortic lymphadenectomy, including the region above the inferior mesenteric artery and up to the renal vein. Furthermore, as for interventions such as radiotherapy or chemotherapy, lymphadenectomy should be subjected to assessments of quality to assure adequacy. Such a trial should also examine differences in morbidity, cost, and quality of life, all of which previous studies have failed to address. Disease-specific survival is but one of many important endpoints because patients will often succumb to other comorbidities. Only by consideration of such factors will a standard of care be identified for the surgical treatment of endometrial cancer. Such a standard is long overdue.

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Composite renal endpoints: was ACCOMPLISH accomplished?

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Currently, the best treatment for renal protection in hypertension titrates drugs to the level of blood pressure wanted by inhibiting the renin-angiotensin-aldosterone system (RAASi).^{1,2} Combination therapy is usually needed and, although many combinations with RAASi have been tested for blood pressure lowering, whether such combinations are equally effective for the most important goal—renal protection—is rarely comparatively studied.

In *The Lancet* today, the ACCOMPLISH investigators³ present the renal outcomes of such a comparative study. ACCOMPLISH examined the effects of amlodipine (calcium-channel blocker) plus benazepril (angiotensin-converting-enzyme inhibitor) versus hydrochlorothiazide (diuretic) plus benazepril on cardiovascular and renal outcomes in about 11500 patients at high cardiovascular risk. Cardiovascular results have been previously published.⁴ The prespecified renal outcome was a composite of doubling of serum creatinine and end-stage renal disease: amlodipine-benazepril was

superior to hydrochlorothiazide-benazepril (hazard ratio 0.52, 95% CI 0.41–0.65). The average systolic/diastolic blood pressure in the overall population was slightly but significantly lower in the amlodipine-benazepril group (0.9/1.1 mm Hg).

This renal outcome of the ACCOMPLISH trial is surprising, because the combination of diuretics with a RAASi is known to enhance the alleged surrogate organ-protective properties of the angiotensin-converting-enzyme inhibitor, such as further lowering of systemic blood pressure, albuminuria, and intraglomerular pressure.⁵ Addition of a calcium-channel blocker to a RAASi does further lower blood pressure but usually does not lower (or can even increase) albuminuria or intraglomerular pressure.⁶ How can we explain that the intuitively better combination did not offer better renal protection in ACCOMPLISH? Perhaps our intuition that such surrogate effects translate into hard renal endpoints is wrong. However, we believe that the ACCOMPLISH trial-design and its interpretation should be more closely examined to verify the validity of the conclusions.

First, there is the bias of the difference in blood pressure during treatment between the tested groups (in favour of the group on the calcium-channel blocker). Second, the study had reduced power due to premature trial termination, and there remains the fact that changes in renal function were based on changes in serum creatinine rather than true measurements of glomerular filtration rate (GFR). However, these biases are trivial compared with a problem in the endpoint—a composite of doubling of serum creatinine and end-stage renal disease. Doubling of serum creatinine is a well-accepted part of a composite renal endpoint, because large long-term changes in GFR are assumed to be related to structural decline in renal function. Most patients show linear loss of GFR over time, and thus doubling of serum creatinine usually reflects a sustained loss of 50% of a

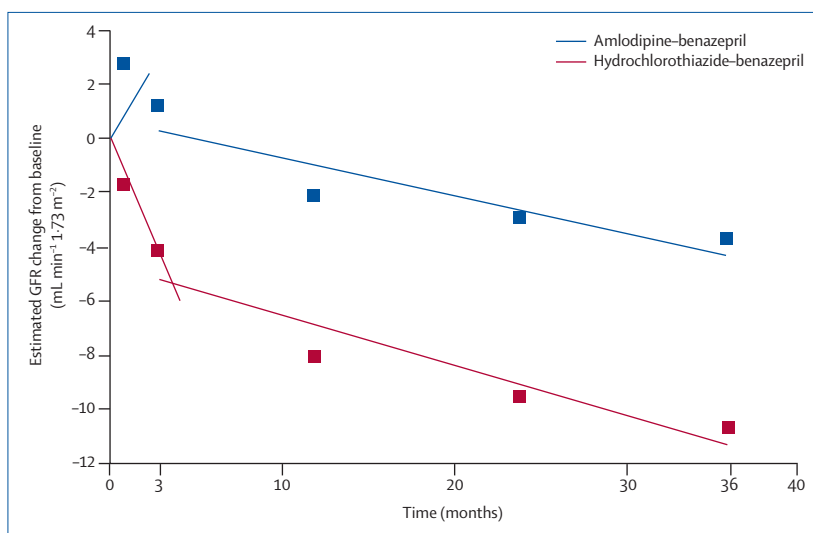


Figure: Short-term and long-term estimated GFR change from baseline in patients assigned to amlodipine-benazepril or hydrochlorothiazide-benazepril
Short-term slope is from baseline to month 3. Long-term slope is from months 3–36. Adapted from data in reference 9.