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Moving Towards Evidence-based Surgery

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In this issue, Nix et al report a small trial comparing open and robotic radical cystectomy with pelvic lymphadenectomy [1]. The authors report the number of lymph nodes removed in a non-inferiority design as the primary end point. Thus, in a comparison of 20 versus 21 patients, we learn that the robotic pelvic lymphadenectomy is not inferior to the open technique in terms of numbers of lymph nodes retrieved.

So, what? At first sight, this trial hardly looks remarkable. Yet, it is remarkable, and it may prove to be an important first step in improving our understanding of how to do trials that will truly advance evidence-based surgery.

The ongoing debate about whether robotic surgery offers meaningful advantages over conventional laparoscopic and open surgery is still largely based on the conflict between the robot advocates' conviction that robotic surgery is simply bound to be better and the conservatives' opinion that the time-honoured open procedure cannot really be improved upon simply with technical gimmicks. These convictions are still seemingly unreconcilable.

A recent systematic review on this question related to radical prostatectomy failed to arrive at any important conclusions regarding differences in long-term outcomes. The only reason for this, the authors agreed, was the lack of good quality data published in the literature [2,3]. Instead, some well-known differences in perioperative factors and parameters were noted among the three techniques.

Unfortunately, there is no longer universal agreement on what constitutes important clinical end points in surgery. Especially since the advent of laparoscopy and robotic surgery, the issues of what is relevant have been obscured. Instead of relying on "hard" outcome parameters (eg, mortality, complications, functional as well as oncologic long-term results), more and more "soft" outcome parameters (eg, cosmetic results, invasiveness, surgery time, estimated blood loss, length of hospital stay) have been introduced into the discussion.

Some factors such as invasiveness and cosmesis are not even defined, although they are used as seemingly valid arguments in the discussion. Other factors cannot be regarded as outcome parameters if the outcome is defined from the patient perspective after convalescence. Perioperative factors such as estimated blood loss and surgery time, or even length of hospital stay, are not instrumental in determining the outcome of a major surgical procedure intended to cure muscle-invasive bladder cancer for the remainder of the patient's lifetime.

I consider these latter outcome parameters to be soft for two reasons. First, they are not really relevant to the ultimate and meaningful outcome for the patient, as defined by disease-free survival and procedure-related long-term morbidity. Second, they have been introduced into the discussions precisely because the new techniques have not really been shown to be better on the hard outcome parameters. Therefore, to keep the discussion going and to promote the new techniques, these soft parameters are highlighted.

We need a clear understanding of and agreement on what really matters for outcome. Complications requiring treatment and resulting in morbidity certainly are relevant to the patient. Recently, there have been good papers assessing complications in a reliable and graded way, such as the Clavien system used in this trial.

Similarly, the comparison of perioperative surgical parameters should be based on better data. In this respect, the trial reported by Nix et al is a promising start [1]. The authors used a randomized approach with equal distribution of surgical risks, which is of great importance in radical cystectomy [4].

What makes this trial truly remarkable is the use of an approach that randomized between two very different surgical treatments. It has long been maintained that randomized trials cannot be done with very different

surgical techniques; indeed, this trial shows that it can be done [1]. We definitely need randomized approaches to exclude the multitude of potential biases that are inherent in just comparing cohorts previously selected for one kind of treatment by criteria outside of the protocol.

The secondary end points reported by Nix et al showed significant differences on univariate analysis in favour of robotic surgery for estimated blood loss, time to flatus, time to first bowel motion and in-house analgesia use [1]. For complications, this must be the future so that comparisons will be more meaningful. There were no differences in the number of complications assessed by the Clavien system, and I believe the authors are wrong in discussing a “trend for fewer complications” with the robotic approach. Clearly, larger numbers are needed.

No doubt the paper by Nix et al [1] will be cited by the advocates of robotic surgery as indicating the superiority of their approach, but this paper does not show that. This trial only shows non-inferiority for the number of lymph nodes. Concerning the reported secondary end points, we must look at clinical relevance. Is a significant difference in time to first bowel motion between means of 3.2 and 4.3 d clinically relevant? Does it matter to the patient 1 yr after surgery? Is the difference between analgesic use of 89 mg (morphine equivalents) versus 147 mg clinically important? I strongly recommend that the latter parameter not be discussed in terms of cost, as that would render the parameter completely meaningless.

When looking at perioperative factors, we should try to reach some agreement on what is clinically relevant. Possible criteria for clinical relevance of an event or a parameter could be whether there is an influence on long-term outcome, including morbidity; whether the event results in a deviation from a clinical care pathway; and whether additional treatments are given (eg, blood transfusions). The important question must be whether the

event is relevant for the patient. Such a discussion would certainly be helpful in clarifying some obscurities in the ongoing disputes over modern surgical technologies. Recently, a prospective case-matched study on robotic versus open cholecystectomy with a follow-up of 12 mo found that the robotic approach lacked any benefits for the patient [5].

In my opinion, the trial by Nix et al proves one important point: that it is possible to do a randomized trial with both robotic and open surgery. The authors are to be applauded for proving that such an approach to evidence-based surgery is possible.

Conflicts of interest: The author has nothing to disclose.

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Reply from Authors re: Oliver W. Hakenberg. Moving Towards Evidence-based Surgery. *Eur Urol* 2010;57:202–3

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We would agree that the most substantial outcomes for a phase 3 surgical trial and for any such potentially curative intervention for invasive bladder cancer is the so-called

hard end point of disease-specific survival at 2 yr and, preferably, at 5 yr [1]. Furthermore, any intervention that seems to compromise such outcomes needs to be scientifically and clinically rejected, especially when one considers the aggressive and often unforgiving nature of bladder cancer. We will certainly carry out this trial to evaluate these most relevant and significant measures of oncologic and clinical success.

Nevertheless, if one is to provide early study and analysis of robotic versus open radical cystectomy (and, for that matter, of any novel intervention or approach) with the level of scientific rigor and quality that our patients deserve, then short-term surrogates need to be used. Such a study can provide early insight and evaluation as to the surrogates' appropriateness and, at least, to their noninferiority to current surgical approaches. In other words, until we can achieve those 5-yr end points, one needs to make

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