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Invasive Bladder Cancer and the Role of Follow-up: Should We Consider the Match Over at Radical Cystectomy or Should We Play for Extra Time?

Renzo Colombo *

Department of Urology, University "Vita-Salute" – San Raffaele, Via Olgettina, 60, 20132 – Milan, Italy

I read the article by Giannarini et al. [1] in this issue of *European Urology* regarding the role of follow-up after radical cystectomy (RC) for invasive bladder cancer, and two aspects emerged that can leave the reader deeply amazed. First, there is evident discrepancy between the socioeconomic impact of regular postoperative follow-up related to the procedure and the few studies specifically designed to define the role of follow-up and its effectiveness. Second, evidence-based recommendations on this topic are lacking, even in international guidelines. Few published studies include analysis of follow-up cost effectiveness after RC [2–6], yet we are all aware that the total cost of a rigorous and articulated schedule of long-term surveillance (5–10 yr) undoubtedly exceeds necessary costs for staging and treatment of bladder cancer. In the major guidelines (eg, European Association of Urology [EAU], National Comprehensive Cancer Network [NCCN], American Society of Clinical Oncology), follow-up is addressed summarily and recommendations are often formulated on empiric basis. In particular, the references are obsolete, based on studies with questionable methods and directed mainly at how to treat recurrences rather than how to identify them early in a cost-effective way.

This lack of clinical evidence and, consequently, recommendations opens the door for subjective follow-up proposals that limit the comparison of experiences not only between different countries but also between different institutions within the same country. And certainly, this situation presents issues not only for follow-up after RC but also for surveillance after major surgery for other kinds of cancers. Difficulty respecting a well-defined programme of postoperative investigation is surely common in most surgical departments.

Among these difficulties is the fact that, frequently, follow-up is not done by the same urologists or by the same department that operated on the patient. Instead, follow-up is done by oncologists to whom patients turn for adjuvant therapy, by private specialists, or by general practitioners. This difficulty can be compounded for the tertiary high-volume centres to which numerous patients living at a distance are referred.

Another difficulty, in my opinion, is the attitude of urologists who think that a surgeon's duty finishes after completion of a technically correct operation. We are used to discussing technical procedures with great enthusiasm (as documented in countless publications), but we are less keen to follow patients postoperatively over the long term. Additionally, we rarely take it upon ourselves to make sure that the patient is motivated to respect regular postoperative follow-up, including rehabilitation programmes (ie, urinary continence and sexual activity), management of stomas, and psychological support.

Another limitation is that many centres, including those with high surgical volume, lack databases specifically designed for follow-up and lack data managers who are able to run such databases. Publications regarding the role of follow-up tend to come from institutes that have used databases for a long time.

All of these issues make me think that trust in postoperative routine surveillance has been reduced. Specifically, what are we expecting from routine follow-up after RC?

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* Tel. +390226437266; Fax: +390226432969.
E-mail address: colombo.renzo@hsr.it.

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Probably, many of us have taken for granted that a rigid schedule of postoperative surveillance could favourably influence the patient's cancer-specific survival. The early identification of both local recurrences and distant metastases, in fact, should represent the basic condition for their adequate treatment, with benefits in terms of survival and quality of life.

The few published clinical experiences of this issue are disheartening or at least controversial. With regard to a recent mono-institutional retrospective study by Volkmer et al. [7], credit should be given for bringing attention to the role of routine follow-up after RC and analysing cost effectiveness. Evaluating a series of 1270 patients who had undergone RC and who were followed for approximately 20 yr, the authors could not show any real advantage in terms of survival at 5 yr. They compared patients who had undergone rigid routine follow-up with those who had undergone some kind of investigation only at the time when their symptoms appeared. In other words, the detection of asymptomatic recurrences would not significantly influence the survival rate. The result is surprising in some ways and is not without relevant impact on clinical practice, as follow-up guided by symptoms has a lower cost than routine follow-up.

The study by Giannarini et al. [1] seems to reaffirm the role of scheduled follow-up, recognising its benefit in terms of survival. It should be noted, however, that this study was not able to define cancer-specific survival at 3–5 yr from RC or from the detection of recurrences when comparing symptomatic and asymptomatic recurrent patients. This aspect remains the paper's major limitation.

Nevertheless, comparison of the studies by Giannarini et al. [1] and Volkmer et al. [7] seems difficult. Different follow-up regimens were adopted, and different populations were included for the type of surgical solutions after RC (eg, only patients with orthotopic bladder substitution in the study by Giannarini et al. [1]) and for pathologic stage of the starting disease. Similarities of the two experiences were the overall rates of recurrence at 5 yr (36.3–38.3%), the most frequent locations of distant metastases (bone: 26–30%; lung: 20%), and the fact that bone metastases were detected more frequently (>80%) at a symptomatic status when compared with lung metastases (20%). Surprisingly, the overall rates of both symptomatic (65%) and local (41%) recurrence were found to be consistently higher in the study by Volkmer et al. [7] when compared with those of Giannarini et al. [1] (50% and 12%, respectively).

Another interesting finding by Giannarini et al. [1] regards the high rate of secondary urothelial tumours (8% for upper urinary tract [UUT] and 13.8% for urethra), as compared with rates reported in the literature [8–10]. Because the study by Giannarini et al. [1] only includes patients with orthotopic bladder substitution (OBS), selected at the beginning for their reduced risk of urethral relapse, this result may only be explained by a more specifically oriented surveillance of the urethra.

Considering that most new urethral lesions and many of those in the UUT can be definitively treated [10], the high rate of those recurrences in Giannarini et al's study [1] might have had a decisive impact on the interpretation of the final outcome. In contrast, if we exclude the secondary urothelial lesions, the literature makes it clear: (1) most recurrences (80%) are detected within the first 24 mo; (2) less than half of all recurrences undergo any form of treatment; and (3) prolongation of survival from the moment of the diagnosis generally does not exceed 6–8 mo, regardless of the treatment adopted. We must be mindful that the oncologic role of follow-up may be minimised by the intrinsic biological aggressiveness of urothelial recurrences.

We must consider that routine follow-up has a recognised role in the preservation of functional outcome, namely, preservation of kidney function and prevention of severe metabolic disorders. For patients with OBS, functional follow-up has a primary role, even in the preservation of satisfactory urinary continence and optimal voiding pattern.

The literature demonstrates a high rate of ureteral (7–14%) and urethral (2–9%) anastomotic strictures as well as renal function deterioration (0.3–27%) [11]. Many of these complications are definitively treatable if detected early on, so the role of functional routine follow-up cannot be renounced. We should give credit to Studer and his group [12] for having promoted rigorous functional follow-up, especially for OBS patients, for a long time.

At this point, it seems reasonable to try to rationalise the follow-up schedule. Computed tomography (CT) scan of the abdomen and pelvis with and without contrast is recognised as the most appropriate imaging test for detecting recurrences. This test, however, suffers from the major limitations of cost and toxicity (high relative radiation level, according to the American College of Radiology) [13]. Presently, no international guidelines make detailed recommendations about priority for the use of contrast or for the timing of CT. The limit related to toxicity might be overcome by using magnetic resonance imaging with and without contrast, but this approach would incur additional cost and reduced reliability [13].

In the new follow-up regimen proposed by Giannarini et al. [1], intravenous pyelogram with tomography/CT is suggested annually for up to 36 mo and only for patients with concomitant multifocal non–muscle-invasive disease at time of RC (who are at increased risk of developing a secondary tumour at the UUT). CT scan of chest, abdomen, and pelvis is suggested every 6 mo up to 18 mo only for patients found to have pT3 lesions or higher or who are node positive (at increased risk for local and distant recurrences). This regimen, seems like a reasonable attempt to optimise follow-up by categories of risk, and the authors must be congratulated on this.

For surveillance of lung metastases, a chest x-ray is still considered an appropriate test with reduced toxicity (minimum relative radiation level) [13], and the 6-mo timing is generally agreed. The value of chest x-ray is not debatable for the detection of many treatable lung metastases and should probably be emphasised more.

Conversely, the role of a bone scan remains controversial. In the present study, 8% of bone metastases were diagnosed, but only 13% could be detected by routine follow-up [1]. The relative rate of asymptomatic bone metastases diagnosed at 24 mo in the study by Volkmer et al. [7] was significantly higher (22%) using extended timing (every 12 mo). EAU and NCCN guidelines do not make recommendations on bone scan and actually do not mention it at all. The new follow-up schedule proposed by Giannarini et al. [1] includes a bone scan every 6 mo just for patients with lesions categorised pT $\geq$ pT3 or who are node positive. I personally believe that bone scan should be guided only by symptoms.

The imaging exam is far more frequently carried out in the course of follow-up with ultrasound of pelvis and abdomen (every 3–6 mo in most cases). However, it has been ascertained that ultrasound has reduced reliability for the early diagnosis of pelvic and retroperitoneal recurrences, and no evidence exists in the literature about the role of this test for diagnosis, staging, or postoperative surveillance. Resorting to ultrasound seems useless during the first 24 mo, when CT is advised. Conversely, there might be consistent benefit after 24 mo, mainly in the context of a functional follow-up.

An additional point for discussion regards postoperative surveillance of urethra. Many urologists contest the usefulness and reliability of cytology, both as a standard measure and after forced diuresis [14,15], and EAU guidelines do not recommend it. I am convinced that many institutions do not include this test at all in follow-up regimens after RC. The study by Giannarini et al. [1] emphasises the role of urethral barbotage cytology every 6 mo as a conditioning factor for oncologic outcome. If it is true that >80% of carcinoma in situ of the urethra can be successfully treated in a conservative way and that urethrectomy, alone or in combination with radio- or chemotherapy, allows for a consistent delay of disease progression, then barbotage cytology should be included in every structured schedule of follow-up after RC. But how many urologists actually know how to adequately perform urethral urinary cytology in patients with both urinary diversion and OBS?

Despite all of these limitations, I think that we should be confident in the role of follow-up after RC for at least four reasons. First, the functional role of follow-up and its intrinsic psychological support for the patient cannot be denied. Second, considering the dramatic progress of imaging for diagnosis, it is probable that in a few years there will be tests for early detection of recurrences. Third, use of surgery for treating small single metastases is increasing, even in multinational protocols, encouraged by minimally invasive techniques. Fourth, target therapy might potentially change the way we face the problem of recurrences after RC. Our job today is to share our experiences, to rationalise everyday clinical protocols, and to keep the doors wide open.

Conflicts of interest: The author has nothing to disclose.

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