



## Cost-Effectiveness of Watch and Wait: What is in the Box of this Organ-Preservation Strategy?

Rodrigo Oliva Perez, MD, PhD

Angelita & Joaquim Gama Institute, Hospital Alemão Oswaldo Cruz, Hospital Beneficência Portuguesa, São Paulo, Brazil

In the present issue of *Annals of Surgical Oncology*, Cui et al.<sup>1</sup> elegantly demonstrate the potential benefits of watch and wait over radical surgery in the clinical scenario of a patient with rectal cancer. Using Markov simulation, they demonstrate that a given patient with stage II/III rectal cancer undergoing neoadjuvant chemoradiation (nCRT) that achieves a clinical complete response (cCR) will be more cost-effectively treated by being enrolled in a watch and wait surveillance program, when compared with radical surgery. This was observed when watch and wait was compared to both low-anterior resection (with a temporary stoma) and to abdominal–perineal resection (APR; definitive stoma). While the study is interesting and definitely adds to the existing evidence supporting organ-preservation strategies including no immediate surgery with watch and wait, a few interesting considerations should be contemplated when taking this into clinical practice.

The study, due to inherent requirements for modeling purposes, includes several assumptions that need to be considered carefully in the setting of paucity of clinical data, particularly related to watch and wait. Some of these assumptions may actually have artificially worsened the watch and wait group in the model, underestimating some of the potential benefits of this approach when compared to radical surgery. The first example here is the assumption that (in the watch and wait group) all patients with local regrowths required definitive colostomy during salvage resection. Considering that local regrowths may be

detected in up to 25–30% (20% was used in the study), this could have affected outcomes as the need for a definitive stoma may be perceived by patients as a clearly worse outcome when compared to sphincter-saving procedures.<sup>2</sup> Data from salvage resection among these patients suggest that many may be treated by sphincter-saving or even rectum-preserving strategies (including transanal local excisions).<sup>3,4</sup> The second example that could also have underestimated the benefits of watch and wait (WW), was the assumption that all patients undergoing radical surgery were fit for adjuvant chemotherapy. This is not true even in randomized controlled trials (RCTs) (where patients are incredibly fit), or in nonrandomized studies where a significant proportion of patients fail to complete the planned adjuvant treatment once radical surgery has been performed.<sup>5,6</sup>

However, a word (or two) of caution must be considered by even the most enthusiastic organ preservation supporter. As the authors suggest by looking at their model, two important features could have been determinants in the outcomes. The model was sensitive to both local regrowth and distant metastases rates. Their estimates suggest that very high local regrowth rates or distant metastases would have been required to change the findings (making surgery more cost-effective than watch and wait). However, one must acknowledge that data on local regrowths, and particularly on subsequent distant metastases (after local regrowth), are scarce and currently largely unavailable. The risk of local regrowth will always be in the box of organ preservation with watch and wait, and should be dealt with caution. Preliminary data suggest that local regrowth may be a risk factor in itself for distant metastases.<sup>7</sup> Even though the risk of distant metastases may be driven by the primary tumor at baseline, tumors incompletely treated by nCRT that develop local regrowth may be biologically worse than their original baseline

counterpart.<sup>8</sup> “Superselection” of resistant clones/subpopulation of cancer cells within the primary exposed nCRT may result in a tumor with greater ability to metastasize. Ultimately, by increasing rates of local regrowths, it is likely that the risk of subsequent distant metastases would also increase, leading to a “snowball effect,” potentially reversing the observed benefits of watch and wait.

Knowing exactly what is in the box of organ preservation is crucial here. Therefore, before we understand the full clinical and biological consequences of local regrowths and the risk of subsequent distant metastases (clearly affecting the outcomes in the present study), modeling may be overestimating the benefits and advantages of watch and wait over surgery. In addition, it will be interesting to understand how the implementation of total neoadjuvant therapy regimens will affect all of these relevant outcomes in determining the cost-effectiveness of organ-preserving strategies.<sup>9</sup>

## DISCLOSURES

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