Are We Denying Distant Control? A Call for Revising the Treatment Protocols of Patients with Ultra-Low Rectal Cancer Who Potentially Require Abdominoperineal Resection

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The advancement of rectal cancer management with the introduction of total mesorectal excision (TME) and the invention of staplers has experienced a dramatic improvement in regards to increasing the rate of sphincter-sparing surgeries and decreasing the rate of abdominoperineal resection (APR). TME has been widely accepted as the best surgical approach that not only decreases the local recurrence considerably but also reduces the rate of permanent stoma. Study results confirmed the reduction of permanent stoma rates from 60.3 to 55.5 and 26.5 %, in the Stockholm I and II trials, respectively. These data were achieved only after the initiation of the TME project via video-based live surgery workshops and histopathology sessions [1].

However, APR is still an unavoidable procedure for low rectal tumors (those located from 0–5 cm from the anal verge), and its use still being performed in many cancer centers in up to 29 % of all rectal tumors [2]. The reason the procedure is unavoidable relates to factors that dictate the type of surgery performed such as the relation of the tumor to the sphincter complex and the ability to achieve clear radial and distal resection.

Low rectal tumors provide challenges for optimal diagnosis and management and also continue to present poor oncological outcome. There are a plenty of evidences from Dutch trial [3], MRC Classic [4], Mercury study [5], and Leeds study [6], and other reports indicated that local and distant control following APR has not provided improvement to the same extent as restorative surgery [7, 8]. Obviously, there are some specific considerations

that have to be recognized during the management of the patients who anticipate requiring APR, and this may explain the worse outcome of APR compared with restorative surgery.

These considerations are related to (1) anatomical factors based on tumor proximity to the anal sphincter complex. Further, lymphatic drainage may follow a different pattern towards iliac and obturator nodes that is usually not included in the routine surgical resection and could play a major role in local recurrence. (2) The gradual tapering of the mesorectum and the lack of a clear resection plan make the conventional surgical approach incapable in obtaining an oncological outcome. Moreover, it has been demonstrated that the mesorectum tapers at the levator sling where adipose tissue between the muscularis propria of the rectum and surrounding tissue disappear. When the conventional surgical approach follows the mesorectum to this tapering point, this would result in a narrow point in the specimen or what is referred to as *waist*, and the tumor will be in danger of exposure with a positive resection margin or even perforation [9]. Quirk demonstrated that positive resection margin is the most significant prognostic factor for developing local recurrence [10]. Furthermore, Nagtegaal reported that almost two thirds of APR specimens have their distal resection margin plan on the sphincter muscle, and in one third of the cases, the plane is intramascular or perforated [3]. (3) Tumor behavior, however, is still unknown. Whether tumor location has an effect on tumor behavior remains elusive, but these tumors tend to have larger tumor size, and higher lymph node positivity. (4) Patient factors include higher BMI, older age, and gender. (5) Surgeon factor non-TME resections may have been performed by surgeons with less specialization in rectal cancer surgery or in hospitals with low volume of such resections [2, 11]. However, it is still unclear whether worse outcome is related to a different

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tumor biology and draining pattern vs inadequate surgical techniques, surgeon factors, and/or patient factors [12].

Preoperative radiotherapy with or without chemotherapy is the current standard of treatment for locally advanced rectal tumors. It has been recognized as a strong influential factor on reducing local recurrence, and all (except an early report of *Swedish trial*) have denied any survival benefit [13, 14].

However, the majority of data have shown that APR continues to have greater local recurrence. Besides, shorter disease-free survival and lower survival were compared with restorative surgery [1, 3, 7]. However, some reports indicated that there are no differences in oncological outcomes when compared stage by stage [15]. The Dutch Colorectal Cancer Group indicated poor survival for patients treated by APR 38.5 % vs AR 56.7 %, $P=0.008$, and higher circumferential resection margin involvement rates for APR (30.4 vs 10.7 %, $P=0.002$) [3]. Consequently, every effort has been considered, using different surgical techniques, cylindrical APR/extra-levator approach/extended APR with cocolicectomy, to achieve a wider negative margin. In addition, there is the use of different modes of radiotherapy to decrease the local recurrence [16]. Inadequate dissection or improper TME appears to be the most influencing factor in determining outcome [17]. Nevertheless, despite all these considerations that have been taken to lower the rate of local failure, still the outcome in this regard of APR group is not equal compared with restorative group.

A retrospective study from Cleveland has shown that after excluding technical and surgeon factors, the results are still uncontrolled. The study concludes that technical factors alone are unlikely to be responsible for the worse outcome after APR [2]. This might be explained by the fact that the APR group has complex risk factors for local and distant relapse that are not comparable to oncological outcome.

By analyzing these data, we can draw attention to the fact that even with modifications of surgical aspects, using the conventional preoperative chemo-radiotherapy for local disease, still we are unable to improve the local and the distant control to that extent. More seriously, no measures have been adopted in controlling distant control, and we probably are still undertreating systemic disease and ignoring this regard.

Moreover, the journey from the time of conventional preoperative radiotherapy with or without chemotherapy (that has been adopted as a radiosensitizer) to surgery usually takes between 8 and 12 weeks. During this time, we probably risk the patient of having distant disease that can result in shorter relapse.

Ultimately, one can raise the issue whether this category of rectal cancer patients (in up to 29 %) is being undertreated

with the conventional preoperative protocols. For this, we should probably revise our clinical practice guidelines towards the management of low rectal tumors with anal sphincter involvement that potentially required APR. Hopefully, future biological studies will be able to address the question behind the worse oncological outcome of the disease and adopt new treatment protocols using different combinations of chemo- and radiotherapy with or without targeted therapy to reverse local failure and better address the distant disease.

Conflict of interest The authors declare that they have no conflict of interest with any financial organization.

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