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Managing Locally Advanced Rectal Cancers: Review of Evidence

Dr. Faraz Badar[1], Mohammad Akram[2]

[1]Senior Resident, Department of Radiation Oncology, Jawahar Lal Nehru Medical College, AMU, Aligarh, Uttar Pradesh, India

[2]Professor, Department of Radiation Oncology, Jawahar Lal Nehru Medical College, AMU, Aligarh, Uttar Pradesh, India

Abstract: ***Management of LARC has evolved from surgery alone to incorporation of radiation and chemotherapy. Here we review the evidence of current practices in management of locally advanced rectal cancers.***

Colorectal cancer is the third most commonly diagnosed cancer worldwide and is second leading cause of death after lung cancer. [1]. In India, it is the fourth most commonly diagnosed cancer in males [2]. Histologically, the predominant subtype of rectal cancers are adenocarcinomas [3]. Locally advanced rectal cancer is a distinct entity and is currently defined as clinical T3–4 (tumor penetrated through the whole bowel wall) and/or N1–2 (involvement of regional lymph nodes), and with no distant metastases. [4]

The management of locally advanced rectal cancer (LARC) has undergone a paradigm shift from the historical standard of maximal surgical resection to incorporation of radiation and chemotherapy as part of multi-modality treatment. Prior to the integration of radiotherapy in management of rectal cancer, the predominant pattern of failure was local recurrence. The landmark trials done in 1980's [5-7] showed significant improvement in outcomes with the incorporation of postoperative radiochemotherapy. This improvement was primarily driven by a reduction in local recurrence rates as well as distant failures.7-year local recurrence rate in GITSG 7175 study was 24% in surgery alone arm, and 11 % in surgery + chemoradiotherapy arm [6]. This translated into an improvement in 7-year overall survival rates from 36% with surgery alone to 56 % with surgery + chemoradiotherapy.

Currently, most popular approach in management of locally advanced rectal cancer is to give concurrent radiochemotherapy in neoadjuvant setting followed a few weeks later by a radical en block resection, the TME surgery (total mesorectal excision) [8]. This approach has its roots in evidence from randomized trials showing superiority of pre-operative radiochemotherapy over post-operative or adjuvant radiochemotherapy in terms of improved local control, decreased long term toxicity, better patient compliance, probability of sphincter sparing surgery and consequent better quality of life [9, 10]. But perhaps the most promising advantage of NARTCT in current times is its potential to fully eradicate the gross disease or achievement of pCR-defined as no residual cancer on histological examination of the surgical specimen. Various studies have reported that after NARTCT complete pathological response (pCR)-is between 15% to 27% [11]. Patients who achieve pCR after NARTCT have better long-term outcomes including local recurrence, overall and disease-free survival [11-14].

Because pCR has been established as a surrogate for improved survival outcomes, researchers have explored the various ways in which treatment response can be improved. There are many ways in which pathological response rates can be improved. Broadly these approaches can be divided in two categories. (i) intensification of neoadjuvant treatment and (ii) increasing the interval between NARTCT and surgery, thus allowing more time for radiation to act. Using induction chemotherapy before neoadjuvant radiochemotherapy, giving 1 or 2 cycles of chemotherapy in the waiting period between NARTCT and surgery, escalation of radiation dose and using multiple chemotherapy agents are some of the ways of treatment intensification. Multiple randomized controlled trials [15-19] have failed to show any improvement in tumor response with the addition of oxaliplatin to concurrent 5 fluorouracil or capecitabine and radiotherapy. Moreover, addition of oxaliplatin led to increase in toxicity.

In the context of radiation dose escalation, multiple studies have explored the role of radiation dose escalation in achievement of better pathological response. Although a dose response relationship has been shown for rectal cancer but optimal radiation dose in neo adjuvant setting is still not known. [20-25]

Patients who achieve a pathologically complete response have been shown to have excellent long-term oncologic outcomes. It follows that if these patients can be accurately identified prior to surgery, they may be considered for non-operative management in an approach that has come to be known as "watch and wait" strategy. Multiple small retrospective series [26-28] have been published whose results suggest that if the patients with clinically complete response can be accurately identified and put on close follow up, immediate rectal surgery can be deferred without compromising on long term oncologic outcomes.

The success of a watch and wait strategy depends on how accurately the radiological imaging tools can identify tumor response. Many researchers have tried to find a radiological tool to assess tumour response accurately before surgery. The most promising radiological tool is MRI which can be used to assess treatment responses to NARTCT [29, 30]. Researchers have found a good agreement between MR predicted tumour regression grades and conventional tumour regression grades as found on histopathological examination. [31]

In conclusion, strengthening of neoadjuvant therapies is the key to improvement in survival of rectal cancer patients.

Radiation will continue to play major role in this setting in the time to come.

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