Clinics in Oncology

Short Communication
Published: 26 Jun, 2017

Organ Preservation; a New Approach in Rectal Cancer?

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Short Communication

Over the past two decades, organ preservation with radio chemotherapy has become a reality in oncology in various sites like anal canal, head neck region. However, management of rectal cancer evolved with treatment intensification in form of total mesorectal excision with neoadjuvant chemoradiotherapy (CRT). Implementation of standard baseline MRI staging enabled a better selection of high risk patients who benefit from neoadjuvant CRT. The recognition that histological features of the resection specimen is a powerful prognostic tools helped to optimize the surgical technique. Loco regional failure rates were reported as < 10% with stage-specific 5-year survival rates between 63% and 77.4%. With these excellent oncological outcomes, it was felt that the results had achieved a plateau but Angelina Hebra Gama and her colleagues, generated the interest in watchful waiting in a subset of patients who have a complete response after neoadjuvant CRT.

Also it was seen that rectal resections are major procedures with substantial morbidity and mortality especially for the elderly and for those with several comorbidities. More than half of patients undergoing TME surgery and neoadjuvant therapies will have long-term complications like anastomotic leakage, pelvic automatic nerve injury, and erectile dysfunction. A proportion of patients who underwent rectal cancer surgery will require either a temporary or permanent stoma.

Multiple studies showed an absence of viable malignant cells in surgical resection specimens after CRT, termed pathological complete response (pCR) in 18.1%-26% of cases. It is widely acknowledged that patients who respond to CRT were more likely to be cured with improved DFS and distant metastatic rates of 89.5% and 7-10.5% respectively when compared to poor responders to neoadjuvant therapy (65% and 26-32% respectively).

"Wait and watch" approach was proposed in Brazil in 2009 and was based on two strategies: firstly, patients were selected after chemoradiation, when restaging had shown a very good response. This allowed organ preservation also for patients with larger tumours, albeit in a smaller proportion when compared to early tumours, as complete responses in larger tumours were estimated to occur in only 15-20%. The second difference was that a local excision was no longer considered essential when the restaging with digital rectal examination, endoscopy and imaging showed a clinical complete response. They prospectively observed a cohort of patients with a cCR with no initial surgical intervention for a period of 5 yrs. Based on a strict surveillance protocol, patients were determined to be responders once they had no evidence of tumor on: (1) DRE; (2) endoscopic assessment; and (3) imaging. The reported 5-year DFS of 71 cCR patients was 92%, compared with the 83% for patients with radical surgery-confirmed pCR ($P = 0.09$). None of the patients developed pelvic LR.

The resurgence of interest in this concept of organ preservation was further evaluated in various studies. Ane Appelt and colleagues reported a remarkable complete clinical response with chemo radiotherapy (40 [78%] of 51 patients) compared with those from previous studies. It was postulated that high response in these patients may be due to intensive chemoradiotherapy regimen, consisting of external-beam radiotherapy of 60 Gy in 30 fractions to the tumour and 50 Gy in 30 fractions to the elective lymph node volumes with intensity modulated radiotherapy combined with oral peroraltegafur-uracil 300 mg/m^2, with both regimens given every weekday for 6 weeks. Moreover, an endorectal brachytherapy tumour boost of 5 Gy was given, which has not been done in previous studies of watchful waiting (eg, the Habr-Gama series in which 50.4 Gy - 54.0 Gy was used with concomitant fluorouracil-based chemotherapy). Two retrospective studies from United states and United kingdom also showed similar DFS and OAS in patients with clinical CR who underwent wait and watch protocol as compared to conventional neoadjuvant chemoradiotherapy followed by surgery.

How about oncological safety of watchful waiting? Patients from expert centres had a local

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Received Date: *21 Mar 2017*
Accepted Date: *04 May 2017*
Published Date: *26 Jun 2017*

Citation:
Bhutani R. Organ Preservation; a New Approach in Rectal Cancer?. Clin Oncol. 2017; 2: 1312.

regrowth rate between 10% and 30%, and the vast majority was easily amenable to salvage resection. Only very few patients suffered from a locally uncontrolled situation and from metastatic disease. The risk of cancer related death was in the order of 2%-3%.

Lymph node status is the most important prognostic factor in rectal cancer. The challenge of a wait and watch policy is to determine whether contemporary imaging modalities adequately evaluate lymph node status in these patients; thus yielding an inferior oncological outcome compared to that of conventional operative management. Deciding not to offer radical surgery based on inaccurate diagnostic tools is the major area of concern before accepting this policy.

The highest quality evidence could be provided by randomized trials comparing standard TME surgery *vs.* organ preservation but will be hardly possible for patients who have a clinical complete response after neoadjuvant treatment, especially when they are facing a rectal amputation. Currently, all available cohort studies are very heterogeneous with varying selection and inclusion criteria, different neoadjuvant therapy schedules, variation in timing of inclusion, differences in follow up schedules and length of follow up. More data and long-term outcomes are needed before this strategy could be safely incorporated into medical practice for suitable patients. The concept of organ preservation like Nigro protocol in anal cancer had been a ground breaking reality and may this might hold true for rectal cancer also. However further work will be needed to identify the patient factors that can predict a pCR. The introduction of molecular techniques could play a substantial role in the identifying selected group of rectal cancer patients who could be offered wait and watch protocol.