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Neoadjuvant therapy in rectal cancer: An ongoing conundrum

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Over two decades ago rectal cancer management was revolutionised with the adoption of total mesorectal excision and the utilisation of neo-adjuvant therapy. Local recurrence rates plummeted to less than 5% with an optimistic view on further advancements in the field. However, in the last 20 years there has been limited further progress in improving the 5-year overall survival rate of patients with rectal cancer, which currently hovers at approximately 65%.

This lack of progress is not reflective of the multitude of clinical trials that have intensively investigated modifications of long and short course neo-adjuvant therapy protocols¹.

Without robust hard data it is impractical to implement a major shift away from standard neo-adjuvant therapy regimens to novel treatment strategies. Thus, the reliance on the trials published by the Swedish and Dutch rectal cancer groups at the turn of the century, as a guide to current therapy decisions^{2, 3}.

The decision to administer neo-adjuvant therapy for patients with rectal cancer depends primarily on the structural components of the disease. There is continued reliance on pelvic MRI to accurately stage patients, and provide anatomical information such as tumoural height and completeness of the circumferential resection margin (CRM). However, patients presenting with the same clinical tumour stage can and do have substantive variation in their clinical outcome. An emerging prognostic factor for patients with rectal cancer is extramural venous invasion (EMVI) which has been shown to be a poor prognostic marker for patients with stage II and III rectal cancer, suggesting that these patients would benefit

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from neo-adjuvant therapy⁴. Total neoadjuvant chemotherapy has been utilised in these cases and is being assessed through ongoing trials^{5, 6}.

Treatment driven by tumour anatomy does not take into consideration the tumoural molecular/genetic features that have significant impacts on prognosis and potential response to targeted therapies. This is highlighted by the classification of colorectal cancers into four distinct subtypes based on gene expression. These consensus molecular subtypes are linked directly to relapse-free and overall survival, as well as generating a basis to select patients for tumour agnostic therapies⁷. In addition to this classification, the importance of the immune system in relation to prognosis has been quantified with the Immunoscore™ providing further depth compared to conventional TNM staging alone by incorporating the impact of the tumour microenvironment on prognosis⁸.

Despite impressive advancement in the understanding of the molecular and immunologic factors impacting prognosis of patients with colorectal cancer and the fact that molecular features offer a deeper insight into prognostication there has been minimal translation of this knowledge into the clinical management of patients. This illustrates a definitive gap between insight into disease process and effective treatment.

To explore the drivers behind treatment pathways for patients with rectal cancer a survey of colorectal surgeons in Australia and New Zealand was undertaken. Key insights were identified from this survey. When provided a case scenario of a T2N0 EMVI positive tumour 44% of surgeons opted to administer long-course chemoradiotherapy (LCCRT) prior to surgery. This response demonstrates that additional structural prognostic information is

penetrating treatment pathways for patients. However, when asked to weigh tumoural factors on the decision to administer neo-adjuvant therapy, both mismatch repair (MMR) status of the tumour and its molecular profile did not impact decision making. Hence TNM staging prevails along with tumoural height and the completeness of the CRM in driving treatment decisions. This again highlights the limited role molecular characterisation has on current decision making, perhaps reflecting a gap in confidence in the current evidence.

Perhaps unsurprisingly the greatest interest in incorporating immunotherapy into the treatment regimen was for patients with metastatic disease. There are however, a group of patients with early-stage tumours that could benefit from neoadjuvant immunotherapy and potentially organ preservation. Immunotherapy is also recognised as an effective treatment modality for patients with MMR-deficient colorectal tumours.

Despite a recent systematic review identifying over 200 studies investigating novel neoadjuvant therapy in the form of alternative cytotoxic agents, dose modifications, and targeted therapies on pathological response¹, progress has been slow. Only one of three protocols are used routinely, with total neo-adjuvant chemotherapy being a recent addition. The lack of consideration placed on the molecular features of colorectal tumours challenges the idea that sequencing the human genome would provide substantial changes to management decisions as treatment decisions are not currently driven by genomics outside of Ras/Braf/MSI status and EGFR monoclonals and immune check point inhibitors. Perhaps this is a systems failure as there is currently no defined strategy available to incorporate molecular subtype stratification into conventional treatments and clearly more trials incorporating molecular data are required. The lack of data results in individual centres

relying on first hand experiences, with subsequent *“chopping and changing”* between protocols.

The ongoing conundrum is how to accurately prognosticate with data we have and the continuing challenge is what agent(s) to give and its sequencing. Opinions are rife but still predominately driven by staging. The gap remains the incorporation of the molecular characteristics of colorectal cancer into treatment paradigms to allow effective targeted therapies. Further trials investigating and validating molecular markers and the advent of novel agents are required but practise is not getting the most from information that is readily available.

References

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This lack of progress is not reflective of the multitude of clinical trials that have intensively investigated modifications of long and short course neo-adjuvant therapy protocols¹. Without robust hard data it is impractical to implement a major shift away from standard neo-adjuvant therapy regimens to novel treatment strategies. Thus, the reliance on the trials published by the Swedish and Dutch rectal cancer groups at the turn of the century, as a guide to current therapy decisions^{2, 3}.

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Neo-adjuvant therapy in rectal cancer: an ongoing conundrum

Running head: Rectal cancer an ongoing conundrum

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