Do we need a new standard of care for colorectal cancer?

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In recent years total neoadjuvant treatment (TNT)—a potent new treatment approach for advanced colorectal cancer that confronts tumors with aggressive rounds of chemotherapy and chemoradiation followed

by surgery to remove the cancerous tissue—has emerged as the standard of care.

"Are we already in the era of total neoadjuvant treatment for rectal cancer?" a recent headline in *The Lancet Oncology* asked.

TNT's strength is that, compared with traditional treatment regimens for the disease that sequence the majority of chemotherapy after surgery, it significantly lessens the chances that cancer will later return and metastasize, though research has yet to show it extends life.

But TNT can be harsh, impacting quality of life for many patients, who suffer side effects ranging from incontinence and sexual dysfunction to cognitive and physical decline. Post-treatment patient surveys underscore that for many, especially younger patients, the costs of TNT can outweigh its benefits.

A new paper published in *Clinical Colorectal Cancer* in January by a team of researchers affiliated with the University of Vermont Cancer Center (UVMCC) takes that patient feedback as a point of departure, and highlights a variety of new colorectal cancer treatments that take into account both a patient's likely health outcome and quality of life factors. Entitled "The Potential for Overtreatment With Total Neoadjuvant Therapy (TNT): Consider One Local Therapy Instead," the work is an invited contribution to a special issue of the journal addressing new paradigms in rectal cancer multidisciplinary care.

To gather information on the new treatment protocols—which offer differing combinations and schedules of chemotherapy, radiation therapy and surgical techniques—the research team conducted a comprehensive review of published studies.

"The lower gastrointestinal team has a variety of new treatment options

to choose from," said the paper's senior author, Dr. Steven Ades, a medical oncologist and associate professor in the University of Vermont Larner College of Medicine. "Our goal is to give context to key advances that have the potential to de-escalate treatment, so clinicians can translate the published outcomes in a way that will help them make decisions in partnership with their patients."

The paper concludes that an approach the authors call Total Definitive Treatment (TDT) is often a viable alternative to TNT in institutions with multidisciplinary teams experienced with the approach. While TNT implies that chemotherapy and radiation therapy will be followed by surgery, TDT acknowledges that chemotherapy and radiation therapy can be "definitive," meaning potentially curative without the need for surgery.

TDT involves a close watch and wait approach to look for whether disease is still present following radiation and chemotherapy, reserving surgery only for patients who haven't responded fully to chemoradiation and chemotherapy and not making it part of the initial treatment plan. Keeping organs intact mitigates many side effects patients mark as bothersome in surveys, including low anterior resection syndrome, or LARS, which saddles them with a range of unpleasant symptoms.

Similarly, for low risk patients, surgery alone may be sufficient without the need for radiation, which can also cause a range of unwanted symptoms.

The researchers suggest clinicians consider the following axiom when approaching patients: one local therapy.

"It can be chemotherapy combined with radiation targeting a tumor, or it can be surgery to remove the tumor, but it doesn't always need to be both radiation and surgery," said the study's lead author, Dr. Chris Anker, a

radiation oncologist and associate professor in the Larner College of Medicine.

TNT as a one-size-fits-all approach for advanced colorectal cancer is problematic, the researchers say, despite its effectiveness in reducing the chance of later metastasis. Other treatments, tailored to the individual and taking into account the importance patients give to quality of life, can be as effective.

Highlighted in the paper is short-course radiation therapy, which decreases the length of radiation from about six weeks to just one. Outcomes between the two different radiation treatment lengths have been found to be equal in the setting of surgery following chemotherapy and radiation. Due to UVMCC's expertise with TDT, it is one of only a few institutions selected nationally to participate in a clinical trial called NOM-ERA, bringing patients the option of short-course radiation therapy followed by chemotherapy with the goal to avoid surgery. The increased convenience and decreased financial burden allowed by this treatment have been popular with patients, and UVMCC investigators are optimistic this will eventually be another standard of care option that further improves patient quality of life.

"It's important for patients and clinicians to make these decisions together," Dr. Anker said, "with full knowledge of all the outcomes, including quality of life outcomes, of a particular treatment. We hope our paper will bring many of the newer treatment options into this dialogue between patient and clinician so they can make an informed decision as a team."

More information: Joanna Socha et al, Are we already in the era of total neoadjuvant treatment for rectal cancer?, *The Lancet Oncology* (2021). DOI: 10.1016/S1470-2045(21)00127-3

Christopher J. Anker et al, The Potential for Overtreatment With Total Neoadjuvant Therapy (TNT): Consider One Local Therapy Instead, *Clinical Colorectal Cancer* (2021). DOI: 10.1016/j.clcc.2021.11.001