Colorectal cancer: Artificial intelligence and its role in surgical decision making

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Abstract
Despite several advances in oncological management of colorectal cancer (CRC), there still remains a lacuna in the treatment strategy, which differs from centre to centre and on the philosophy of the treating clinician which is not without bias. Personalized treatment is essential for the treatment of CRC to achieve better long-term outcomes and to reduce morbidity. Surgery has an important role to play in the treatment. Till today, the surgical treatment of CRC is decided based on clinical parameters and investigations and hence, likely to have judgmental errors. Artificial intelligence (AI) has been reported to be useful in the surveillance, diagnosis, treatment and also in the follow-up with accuracy in several malignancies. However, it is still evolving and yet to be established in surgical decision-making in CRC. It’s not only useful preoperatively but also intraoperatively. AI helps to rectify the human surgical decision when clinical data, radiological, laboratory parameters are fed into the computer, and may guide correct surgical treatment.

INTRODUCTION
Mr. Alan Turing in 1950, hypothesized that A machine can also think like as a human being in his book entitled “Computing Machinery and Intelligence”. [1] The term “Artificial intelligence (AI)” was later coined by John McCarthy in a
summer workshop\textsuperscript{[1,2]} AI has evolved from simple task to more complex task similar to a human brain.\textsuperscript{[1]}

AI has proven its worth in various day-to-day life, human requirements, including health care (health tracking devices)\textsuperscript{[3]}, automobile (autopilot)\textsuperscript{[4]}, banking and finances (chatbots, robo-traders)\textsuperscript{[5]}, surveillance (CCTV cameras), social media, entertainment, education, space exploration, industries (aluminum, dairy)\textsuperscript{[6,7,8]}, disaster management\textsuperscript{[9,10]}. One the recent example is the efficient production of facemasks during COVID-19 pandemic\textsuperscript{[11]} (Table 1). Its potential has been exploited in various fields of medicine, including online appointment scheduling, online check-in in hospitals, digitalization of medical records, follow-up and immunization reminder, drug dosage algorithm and adverse effect warnings during the prescription of multidrug combinations. Besides this, its application in the field of oncology is immense. AI is assisting in generating new approaches for cancer detection, screening of healthy subjects, diagnosis, classification of cancers using genomics, tumor microenvironment analysis, prognostication, follow-up, and new drug discovery\textsuperscript{[12,13,14,15]}.

Colorectal cancer (CRC) is one of the most common types of gastrointestinal tract malignancy and is the fourth most leading cause of cancer death globally\textsuperscript{[16,17]}. AI has been used to facilitate screening, diagnosis (colonoscopy, advanced endoscopic modalities, imaging), genetic testing, treatment (chemotherapy, radiotherapy, robotic assisted surgery)\textsuperscript{[18]}. New research and developments are required for better patient management to improve the outcome.

In the past decade, several developments have taken place in the management of CRC e.g. revised anatomy of rectum and concept of TME by Bill Heald\textsuperscript{[19]}, concept of complete mesocolic excision (CME) and central vascular ligation(CVL) by
Hohenberger[20] for colon cancer, imaging and staging techniques, introduction of staplers[21], newer chemotherapeutic agents and biologicals, radiation therapy and mode of surgery (laparoscopic and robotic surgery)[22,23] have significantly improved the outcome and sphincter preservation. However, there still remain numerous challenging issues like, accurate preoperative diagnosis, staging, individualized and personalized treatment planning, intraoperative challenges to minimize complications and improve the surgical outcome. Newer tools of AI have been used in various fields of medicine, including drug development, health monitoring, managing medical data, disease diagnostics, digital consultations, personalized treatment, analysis of health plans, medical, and surgical treatment[24] and is coming faster to have its role in surgery and surgical decision-making.

Two common fields of the AI used in medicine are: virtual and physical field[25]. Virtual field is commonly used in medical imaging, clinical diagnosis, treatment, drug research and development. Surgical and nursing robots are the part of physical fields. Because of ongoing innovations in AI, it is being used widely in medicine, both for diagnosis and management of tumours. AI has its significant role to play in CRC, at various stages and reported to have improved the 5-year survival. The subsection of AI used in medicine is deep learning (DL), which is responsible for widespread application of AI[26]. This method encompasses all the concepts of AI and is based on artificial neural networks (ANN), which is inspired by the neurons in a biological brain. DL involves application of training a specific task on a larger data, extracting information from them, and using them for future predictions about these tasks, through flexible adaptation to the new data. Recently, DL has been used to predict cardiovascular risk based on retinal images[27], classification of skin lesions[28], mammogram-based breast cancer detection[29] and oesophageal carcinoma[30]. However, application of AI in surgery is challenging, as unlike the use of static images, surgery includes dynamic procedural data like the patient clinical parameters, different devices used, knowledge of clinical guidelines and from the experiences[31]. The uses and applications of various branches of AI in medicine as well as other fields are shown in Table 1.
In 2007, IBM began development of Deep QA technology (Watson). In 2017, Artery’s medical imaging platform was the first FDA approved cloud-based deep learning application in healthcare for cardiac disorders, which was faster in giving results as compared to the professionals (15 s vs 30 s)\(^{[32]}\). The US-FDA approved, “GI genius” in the year 2019 which is the first device based on machine learning to aid clinicians in detecting polyps, or tumours during colonoscopy.
This paper reviews the current status of AI in CRC surgical decision-making and its future implications.

**Uses of AI in Gastrointestinal disorders and colorectal cancer:**

AI is progressively being used in the understanding of gastrointestinal (GI) diseases\(^{[33-35]}\). Imaging such as X-ray, computed tomography (CT) scanning, magnetic resonance imaging (MRI) or endoscopic image is being used for diagnosis\(^{[36-39]}\). The application of AI has led to early detection of intestinal malignancies or premalignant lesions, and inflammatory or other non-malignant diseases or lesions\(^{[40]}\).

With IBM Watson for Oncology (WFO), AI has found its increasing role in oncology therapy. It has been used in several malignancies like carcinoma breast, carcinoma lungs, gastric cancer, colon and rectal cancer etc. Initially, MSKCC, New York, United States has started the use of WFO machine learning. WFO uses, Natural language processing and clinical data from multiple resources (treatment guidelines, expert opinions, literature and medical records) to formulate treatment recommendations\(^{[41]}\). A recent meta-analysis\(^{[42]}\) had shown highest concordance between WFO and MDT in carcinoma breast and lowest in carcinoma stomach. Manipal Comprehensive Cancer Centre (Bangalore, India) has implemented WFO for treatment in 250 CRC patients\(^{[43]}\). There was a concordance in 92.7% of rectal and 81% of colon cancer patients between WFO and MDT recommendations\(^{[43]}\).

**AI in Colorectal cancer:**
AI is used in the diagnosis and treatment of colorectal polyps and cancer. In colorectal cancer, it helps in diagnosis, staging (lymph node or liver metastasis), preoperative treatment planning, response to treatment assessment, intraoperative assistance, postoperative prognostic information etc. \cite{44,45,46}.

1. **AI in preoperative surgical decision making: staging and planning:**

   After diagnosis of CRC is made, the most important consideration is staging to determine a further plan of management, whether upfront surgery, neoadjuvant treatment, or palliative treatment.

   In locally advanced rectal cancer, preoperative chemoradiotherapy is known to reduce the local recurrence. However, selection of patients is essential to avoid unnecessary complications due to overtreatment. Therefore, there is a need for a system which can differentiate between T2 and T3 rectal cancers. Kim \textit{et al.} (2019) used convolutional neural network (CNN) models to distinguish T2 from T3 Lesions from MRI with an accuracy of 94\%\cite{47}. Similarly, Wu \textit{et al.} also used CNN to stage rectal cancers\cite{48}.

   In addition to its role in preoperative imaging, AI provides faster interpretation compared to radiologists (20 s vs 600 s) in the detection of lymph node metastasis in rectal cancer\cite{49}. Preoperatively, PET CT is commonly used in case of indeterminate lesions on CECT, to find out the potentially curable M1 disease (NCCN version 3.2021). Recently, application of AI has improved the sensitivity and specificity of detection of pulmonary nodules\cite{50}. AI can also be used to reconstruct the area of interest from two-dimensional (2D) data obtained from imaging and endoscopic findings to generate a three-dimensional (3D) structure for better delineation of the tumour in relation to the surrounding vital structures which may be useful in preoperative surgical planning\cite{51}.

   This is extremely useful in determining which patient will require a pelvic exenteration or which patient will require a lateral pelvic lymph node dissection. This is also useful to safeguard the important surrounding structures during surgery to reduce the postoperative morbidity and mortality related to it.
In colon cancer, clinical evidence of bulky nodal disease or T4b lesion entails neoadjuvant therapy (NCCN guidelines version 3.2021). It is also recommended that the presence of nodal involvement in T1 cancer requires colectomy and lymphadenectomy. Kudo S et al (2021) have applied machine learning principle, ANN in 3134 patients with T1 CRC based on the patient’s data on age, gender, tumour size, location, morphology, lymphatic and vascular invasion, and histologic grade to predict nodal involvement.\(^5\)\(^2\)\(^2\) ANN model was significantly better in lymph node metastasis detection compared to guidelines (AUC-0.83 vs AUC-0.73, p-value= 0.005). So, these patients can be subjected to upfront surgery and lymphadenectomy instead of endoscopic treatment. In a meta-analysis by Bedrikovetski et al using 17 studies (12 used radiomics models and 5 used deep learning models) concluded that, AI was more efficient than radiologists in predicting lymph node metastasis.\(^5\)\(^3\) Similarly, AI was found to be better in detecting metastatic nodes as compared to conventional PET CT imaging.\(^5\)\(^4\)

2. AI in intraoperative surgical decision-making:

Execution of a surgery depends upon the operating skill and ability of decision making. In 1978, Dr. Frank Spencer, a cardiovascular surgeon, mentioned that “a skillfully performed operation is about 75% decision making and 25% dexterity.”\(^5\)\(^5\) The decision making can be both technical or non-technical which impacts patient outcome. Studies of surgical errors have shown that over half of the adverse events are due to cognitive errors.\(^5\)\(^6\) But surgical training is more focused on skill training rather than decision making as it is a challenging task to train.\(^5\)\(^7\) Decision-making skills may vary with experience of operating surgeons.\(^5\)\(^8\) Thus, improving the quality of surgical decision-making could help to improve the outcome of surgery.

Decision making is a three-step process, i.e. assessment of the situation, action-taking, and re-evaluation of the action’s consequences. AI has been used as a decision-making aid in a variety of fields, both in medicine and also in surgery.\(^5\)\(^9\),\(^6\)\(^0\). AI can help surgeons to assess a given situation (e.g. retrieving better data about a clinical situation), the types of actions taken (e.g., through decision suggestion), and the process
of re-evaluating the impact of the decision taken. So, it can be achieved in 3 different ways, i.e. (1) retrieving data and experience from similar clinical scenarios and to supplement sensory input during minimally access surgery (MIS) which are not available compared to open surgery, (2) intraoperative pathology assessment, tumour margin mapping, tumour classification and tissue identification, (3) suggestion of steps of surgery.

a) Identification of surrounding structures:
Harangi et al used an artificial neural network model to distinguish ureter from uterine artery during laparoscopic hysterectomy with 94.2% accuracy⁶¹. Similarly, Quellec et al applied a system of retrieving related videos of retinal surgery and subsequent steps were followed during surgery to minimize the risk of injury⁶². Various studies have shown improved detection of vital structures during laparoscopic cholecystectomy to prevent bile duct injury using AI (Madani A et al⁶⁵, Pietro Mascagni et al.⁶⁶, Tatsushi Tokuyasu et al.⁶⁷). Table 2 highlights the studies where AI was used for identification of vital structures.

In CRC surgery, AI can be used to detect nearby vital structures (nerve plexus, presacral venous plexus, ureter, bladder, urethra, prostate, seminal vesicles), lymph node metastasis (lateral pelvic nodes, nodes near the root of inferior mesenteric artery), determination of the margin of resection, vascularity and adequacy of anastomosis.

Augmented reality (AR), augments surgeons’ intraoperative vision by providing a semi-transparent overlay of preoperative image on the area of interest⁶⁸. It has been used in several GI surgical procedures like laparoscopic splenectomy⁶⁹ and pancreaticoduodenectomy⁷⁰. AR can be applied to CRC surgeries to identify and preserve the nearby vital structures.

b) Deciding the level of resection:
In CRC surgery, determination of margin status is important to decide the level of resection and consideration for the feasibility of an anastomosis or the creation of a
stoma. Margin status can be obtained with “optical biopsy” (in vivo diagnostic imaging), which can avoid time-consuming resection and frozen section analysis. Fluorescent guided surgery is evolving, and it has shown promising results in determination of liver or peritoneal metastasis, anastomotic perfusion, detection of sentinel nodes, ureter, nerve, intraoperative detection of primary and recurrent lesion during colorectal cancer surgery [71]. Such a concept can be extrapolated on to AI for more efficient performance. Modalities used for intraoperative optical biopsy are CLE (confocal laser endomicroscopy), hyperspectral imaging (HSI), and optical coherence tomography (OCT), contrast enhanced ultrasonography (CEUS). There are several studies where these modalities have been used to distinguish abnormal epithelium from normal one, with the help of AI (Table 3). Using HSI, Winkel et al have reported 94% accuracy in distinguishing carcinoma from adenoma and healthy mucosa using ANN on post-resection of colonic lesion during surgery [72]. A couple of experimental studies have shown that laparoscopic HSI can be used to distinguish malignant tissue in CRC from normal tissue. These modalities can be used to help in surgical decision-making in the CRC as revisional surgery can be done intraoperatively rather than waiting for frozen section or final histology avoiding another surgery [73,74].

c) Deciding the site of anastomosis:
Studies have shown the incidence of colo-colic and colo-rectal anastomosis leak to be 3.3% and 8.6% respectively [78] and has adverse clinical outcome and economic burden [79]. It can lead to anastomotic site stricture, recurrence of malignancy and poor evacuatory function. The literature have shown poor predictive value of surgeons’ perception of possible anastomotic site leak that led to search for other methods like use of indocyanine green (ICG) [80]. The robotic platform provides inbuilt near infrared (NIR) camera for assessment of vascularity at the resection margin and to reduce anastomotic site leakage [80]. A study by Mazaki J et al, where auto-artificial intelligence was used to develop a predictive model for anastomotic leakage and result showed that triple-row staplers can decrease the leak rate [82]. There is an ongoing study by Taha A et al known
as PANIC study (The Prediction of Anastomotic Insufficiency risk after Colorectal surgery) which utilizes machine learning principles to formulate an algorithm for prediction of anastomotic leak following colonic (PANIC-C) or colorectal (PANIC-R) anastomosis. The results of the study may focus more light which is expected to be available by the end of year 2022[83].

*d) Helping in operative step suggestion:
Operative step suggestion in CRC is at a developmental stage and in the literature, AI has been used in cataract surgery and spinal cord surgery with satisfactory results. Tian et al developed VeBIRD (Video-Based Intelligent Recognition and Decision system) to track and classify the cataract grade on videos of phacoemulsification surgeries[84]. It helped to decide the amount of ultrasonic energy needed to emulsify a cataract based on the grade, so a less experienced surgeon can perform the procedure with as much efficiency as that of an experienced personnel. Somatosensory evoked potential (SEP) is used during spinal cord surgeries to detect spinal cord injury. A decrease in SEP value needs to be confirmed with awakening the patient and checking spinal cord function and this decrease in SEP can be due to the effect of anaesthesia. Fan et al applied support vector regression and multi-support vector regression to distinguish spinal cord injury from anaesthetic effect[85]. Similarly, in CRC surgery such methods can help to find the area of interest to formulate standardized resection and differentiate intraoperative lymphorrhea from ureter or bladder injury using AI.

Colorectal cancer surgery requires accurate and judicious preoperative decisions to optimize the outcome of surgery (personalized treatment). The decision can be augmented by the use of AI which is expected to be precise and without errors. It can assist in imaging, tissue diagnosis and staging before surgery. It can be used preoperatively to choose patients for neoadjuvant therapy and those requiring upfront surgeries. Intraoperatively, it helps in the identification of tumour tissue (to determine the margin of resection), metastatic lymph nodes (for the extent of lymphadenectomy)
and important surrounding structures. Its assistance is also useful in assessing the adequate vascularity at the anastomotic site which can decrease the postoperative anastomotic leak and thereby reducing the morbidity and mortality.
Like the application of AI in several domains of medicine and health, it may play significant role in surgical decision making, enhancing the outcome, in addition to diagnosis (imaging, endoscopy, tissue diagnosis).

**FUTURE IMPLICATIONS:** Future is promising, where AI is likely to play a significant role in reducing the bias of MDT in deciding the treatment strategy, reduce the diagnosis and planning time with uniformity and with no or minimum error. The day is not far, when the surgical world may be able to find a personalized surgical treatment for each and every patient of colorectal cancer, with improved intraoperative technical execution and reduced complications. The overall time taken in the management of CRC will be reduced, the treatment will be standardized and the outcome will be maximized.

**CONCLUSION**
Role of AI in CRC is currently limited to preoperative staging, assessment of surgical resection margins and anastomotic site. It’s application to surgical decision making is still evolving and the literature is very limited, however, the future is promising.
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