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EDITORIAL

Whither the coloproctologist of the future? Returning to the kindred spirit of the barber-surgeon

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It is not science fiction that the recent advances in technology, biology and pharmacology are contributing to the demise of the notion of the contemporary colorectal surgeon. Both nanotechnology and the microchip have presaged the development of artificial intelligence (AI), robotics, big data, advanced imaging and three-dimensional (3D) printing each of which along with the elaboration of the human genome has heralded a technical revolution that is well underway. The role of the surgeon is becoming progressively subordinated by technology that is capable not only of earlier diagnosis but of disease eradication. These developments along with a greater reliance on machines that standardize procedural quality will result in an environment which is less dependent upon individual surgical skill.

In a specialty now so driven by instrument innovation, the interventional role of the surgeon is diminishing on many fronts with the advance of a variety of divergent disciplines, particularly in interventional radiology and endoscopy [1]. Even though this future colorectal surgery is built with the bricks from its traditional historical edifice, knowledge concerning the chronological progression of the specialty manifestly supported by a highly skilled practice may be less pertinent for instructing cases that will be logged into virtual spaces and remotely managed by AI-directed robots. The future body will be transparent and will house molecular detectors designed to create extremely sensitive body holograms for cancer diagnosis at the cellular level. In colorectal cancer (CRC) management, machine learning platforms such as the IBM Watson for Oncology are already harnessing huge databases of clinical information, proteomics and metabolomics, improving diagnostic accuracy and contributing to the implementation of algorithm-based management protocols [2].

Outside of the operating theatre, nanotechnology will increasingly insinuate itself into colorectal practice for use as magnetic nanoparticles, quantum dots and nanoformulations that facilitate tumour diagnosis by recognising tumour cells [3]. Nanoligands will function as drug delivery vehicles, efficient radiosensitizers and agents for photothermal anticancer therapies, proving highly sensitive in cancer diagnosis when linked to imaging contrast molecules and cancer biomarkers. Prognostic information provided by individual tumour analysis affords the opportunity of personalized patient care, with *BRAF* and *KRAS* mutations acting as indirect markers of anti-EGFr drug resistance in advanced disease. Molecular identification of genes encoding microsatellite instability (MSI) and mismatch repair (MMR) may in localized disease categorise distinct immune subtypes with different prognoses and treatment sensitivities. Here, tumours with elevated MSI are implicated in the complex processes around antigen presentation and immune editing that occurs within the tumour infiltrating lymphocyte (TIL) population and which regulates response rates to the cardinal checkpoint inhibitors (CTLA-4 and PD-1/PD-L1) that are now more routinely used in chemoresistant cases.

Selected immunotherapies can now be more readily tailored to the identifiable somatic mutation burden favouring a Th1 lymphocytic infiltrate. This approach can upregulate the expression of a variety of immune checkpoints so as to negate some of these mechanisms employed by the tumour in escaping immune destruction. The isolation of T cells from patients which are then modified to target specific tumour-associated antigens (TAA) holds the prospect of individual chimeric antigen receptor (CAR)-T cell therapy [4]. This approach has been used successfully in the

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treatment of B cell malignancies, although solid tumours where there are hypoxic cores, considerable heterogeneity in TAA expression, sparse TIL populations and immunosuppressive microenvironments pose significant challenges. Given the complexity of these treatments, the logistical and economic issues surrounding this type of personalised therapy need to be addressed [5]. Second- and third-generation therapies using this approach have added costimulatory domains, cytokines and transcription factors for recognition, each of which has been targeted to the tumour milieu. Future targeted cell therapies will generate multiple antigen-specific CAR-T cells, use universal CAR-T cells that could be extracted from an allogeneic donor pool and humanise single-chain variable fragments (scFv) for more effective T cell stimulation. The ancillary use of AI will overcome some of the current limitations of this technology by identifying and manufacturing key genetic sequences and by detecting clinicopathological patterns from pooled data sources that have been shown to be specifically predictive of tumour responsiveness [6].

The widespread use of the "wait-and-see" policy introduced by Habr-Gama in 2004 for the treatment of rectal cancer [7] will continue to reduce the number of rectal excisions, as will the increase in total intensive neoadjuvant treatment programmes. Even if this extended neoadjuvant approach has limited demonstrable benefits in terms of disease- and metastasis-free survival, the number of patients undergoing organ preservation will undoubtedly increase [8]. Our improved understanding of the pathogenesis of hereditary CRC has led to the expansion of gene panel sequencing of a wide selection of cancer predisposition genes. This allows the use of peptide vaccines that exploit critical recurrent frameshift-induced neoantigens that are activated through defective MMR machinery [9, 10]. Second-generation vaccines potentially targeting TILs that recognise and eliminate MMR-deficient cells could then be developed [11].

A much better knowledge of all the cascade of events involving inflammation has led to significant advances in the medical treatment of inflammatory bowel diseases. Immunosuppressants and a range of monoclonal antibodies directed against tumour necrosis factor (TNFα; infliximab, adalimumab, golimumab, certolizumab pegol), anti-interleukin (IL)-12/IL-23 (ustekinumab), anti-IL-23 (mirikizumab), anti-IL-6 (sarilumab) and anti-IL-13 (tralokinumab) have achieved a significant reduction in the number of patients requiring surgery. These new agents have improved the final outcome in cases that did not respond to conventional treatments, which usually included corticosteroids, aminosalicylates and first-generation immunomodulators (azathioprine, 6-mercaptopurine and methotrexate). Nevertheless, there are still conflicting reports on whether the absolute numbers of surgical interventions for Crohn's disease have changed in the modern era of biologic therapy. Whereas one Swedish study reported a lower incidence of complicated disease and surgical intervention [12], another population-based study from Ireland showed no change over time [13]. Despite these differences, others have shown that there has been more of a demographic shift in hospitalised cases towards patients who present with medically unmanageable stenosis and malnutrition [14]. In this regard, Mege and colleagues in New York have demonstrated over a prolonged period of time that there is an overall decrease in the percentage of the fibrostenosing phenotype accompanied by a concomitant increase in the number of penetrating cases requiring operation [15]. From the surgical viewpoint, there has also been a worldwide adoption of laparoscopy for the management of Crohn's disease. Successful use depends upon the complexity of the presentation with open conversion still often necessary for extensive adhesions, pelvic fistulae and some complicated inflammatory masses [16]. In ulcerative colitis (UC), improvements in the control of disease activity have reduced the number of surgeries for steroid-refractory disease [17, 18], with a concomitant shift in elective cases towards treatment of dysplasia and supervening cancer. Improvements in our ability to favourably manipulate the microbiome may change the natural history of these diseases and potentially influence their surgical indications, although preliminary work with faecal microbiota transplantation (FMT) has had only limited endoscopic and clinical success [19].

Within the colorectal ambit, complicated acute diverticulitis remains one of the most frequent urgent pathologies, but its management has changed markedly. More young patients are now treated on an outpatient basis or with percutaneous abscess drainage, if appropriate. In cases presenting as perforations with more advanced degrees of peritonitis, most resections are performed laparoscopically and completed with a primary anastomosis [20]. Despite the higher rate of disease recurrence and subsequent hospital admission after an acute episode of diverticulitis, the number of elective colonic resections is decreasing [21]. The decision to proceed to elective surgery performed as a minimally invasive procedure is then individualized in accordance with its perceived risk–benefit ratio.

Proctologists also work in a changing environment in which many generalists refer patients with complicated anal fistulae to specialists in the discipline who have accumulated expertise in new continence-preserving treatments. After appropriate high-resolution imaging, initial treatment may consist of simple drainage of collections without extensive wound exploration and referral for one of the newer surgical procedures that have demonstrated a lasting success. These less destructive options which have been elucidated and compared in a position statement by the Italian Society of Colorectal Surgery (SICCR) [22] allow a choice between endofistular procedures (setons, laser ablation,

video-endoscopy, biologic glues, plugs, stem cell therapy) and perifistular treatments (over-the-scope clip [OTSC®], ligation of intersphincteric fistula tract [LIFT], transanal opening of the intersphincter space [TROPIS]). Recently, Litta et al. [23] have shown that the fistula tissue has an excessive infiltration of IL-17-expressing CD8 T cells, with a concomitant decrease in the macrophage 1/macrophage 2 ratio. This specific shift in the balance of inflammatory cytokines and growth factors within the wound microenvironment differentiates chronic fistulae from healthy tissue, supporting the notion that in the future immunotherapy directly targeting cytotoxic CD8 T lymphocytes will likely diminish the role of the surgeon even further.

Operative treatments for chronic anal fissure have largely disappeared with haemorrhoid practice that monitors matched subgroup outcomes and which employs less invasive operative options and novel endoanal devices that target the haemorrhoid vasculature. For patients presenting with significant faecal incontinence and a demonstrable sphincter defect, the management has shifted from sphincter repair to neuromodulation. The future of this field lies with a variety of regenerative therapies that include the local infusion of progenitor stem cells and trophic factors. Many of the pelvic floor disorders continue to be primarily managed with non-operative therapies that focus on reinforcement biofeedback loops and that are supported by intensive psychological counselling. If a structural defect can be demonstrated, no doubt it will be repaired by robots.

In this rapidly moving landscape, how does the coloproctologist adequately and safely prepare? When interviewed about the pitfalls and the favourable aspects of training, colorectal residents and graduates reported that they are drawn to the dynamism of an evolving specialty although many expressed the desire for additional exposure to robotic training platforms and more advanced anorectal and pelvic floor experience [24]. The increase in complexity of care explains calls for an expansion of pre-existing learning modules and an earlier introduction of specialized colorectal training into the surgical apprenticeship. As the number of conventional surgical interventions continues to fall the structure of training needs re-evaluation. Learning will come from every quarter, preserving the traditional tools alongside the newly acquired skills afforded and supplemented by augmented reality devices, AI, wearable sensors, telemedicine, gene analysis and 3D printing and modelling.

We are witnessing the rapid growth of robotic colorectal surgery that permits surgeons to reposition patients and ports without the need for a re-set-up. Advances in instrumentation and visualization have made multi-quadrant procedures possible. Targeting antibodies, molecular-labeled tumour markers and fluorescence capabilities built into newer systems have assisted real-time on-table assessments of anastomotic perfusion, ureteric identification, the determination of residual peritoneal cancer deposits and isolation of sentinel lymph nodes. The robot of the future will be mobile and driven by machine learning so as to provide a uniformity of surgical performance where agreed standards of training will analyze the proficiency of specific tasks rather than rely on case volume. Robots will eventually operate with autonomy and their untethered miniaturized microscale progeny will be programmed with controllable nanoscale components that will be innovatively fabricated, actuated and powered for navigation down to a cellular level. These nanoscale robots will reach relatively inaccessible places within the body with the capacity to perform precision biopsies and retrieval, transport targeted drugs, image and ablate tumour deposits and even carry out rehabilitating surgeries [25, 26].

We are only at the beginning of the influence AI will impose. It will tailor clinical decision-making and treatments preoperatively, contribute to evidence-based risk assessment, hone imaging radiomics to better predict pathological responses to neoadjuvant therapies in rectal cancer cases and direct those best managed by watchful surveillance. New AI engagement is currently able to set the standards for intraoperative performance with robotic and laparoscopic instrumentation, streamline enhanced postoperative recovery algorithms and digitally support pathology diagnosis [27]. Imaging informed by AI will complement 3D planning and printing creating surgical models that already expand surgical training, preparation and simulation and that will be used for more complex and currently unimagined cases [28]. Presently, 4D printing biotechnology aims to develop tissue constructs with the facility to transform their underlying shape and inherent characteristics under physical, chemical and biological stimuli so as to repair, regrow or replace almost any tissue [29].

Clinicians of the future will also have ready access to genomic services that will be integral in patient management. These routine facilities will expand the risk reduction of heritable cancers, accurately detect cell-free deoxyribonucleic acid transcripts from a range of cancers with a single blood test, support personalized anticancer therapy and provide a real-time molecular analysis in the operating room of the completeness of a precision oncologic resection. With advances in stem cell technology and tissue engineering, regenerative medicine will create functional substitutes for almost any type of damaged tissue or organ. This will pragmatically change the face of transplantation and extend the role of organs normally considered ineligible for use. One challenge presently is the integration of biologic and synthetic scaffolds that can be secondarily seeded with vascular stem cells to form functioning minimally immunogenic xeno-human composite tissues.

For surgeons to evolve we will need to continuously embrace learning opportunities and innovations which appear expectedly or otherwise, from many disparate

disciplines. We have seen those remaining old masters, (our teachers from a bygone era who are also subject to these existential rules), either adapt and survive or withdraw from the newly defined surgical practice. For those entering coloproctology the future domain of surgical intervention may become somewhat limited and dominated by relatively minor procedures. Perhaps there is in this scenario some similarity with the barber-surgeons of old. But unlike these forebears, our anticipated surgical sphere of influence will expand. The future surgeon will quarterback disease screening and endo-management, accommodating a tailored care that keys in a personalized patient cellular profile and matches this to the latest evidence-based treatment protocols. Many surgeries will be painless and scarless standardized events remotely performed by self-governing machines operating in augmented, AI-driven environments to seamlessly restore or replace the anatomy with bioengineered prostheses.

Regardless, however, of the technological advances already made and of those yet unforeseen, there are some things a robot, (even one fully enhanced by machine learning), cannot accomplish. Patients are more than the mere sum of their parts. They are an amalgam of neural, endocrine, immune and psychic elements requiring a comprehensive and holistic approach in order to achieve a successful outcome [30]. The capacity to integrate and to practically apply all of this accumulated wisdom for the benefit of our patients remains the goal in any era of medical science. Aspiring to this universal objective, we will still need the compassion and humanity of a competent colorectal and anal surgeon.

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Declarations

Conflict of interest The authors state that they have no conflicts of interest that should be declared that pertain to this article.

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