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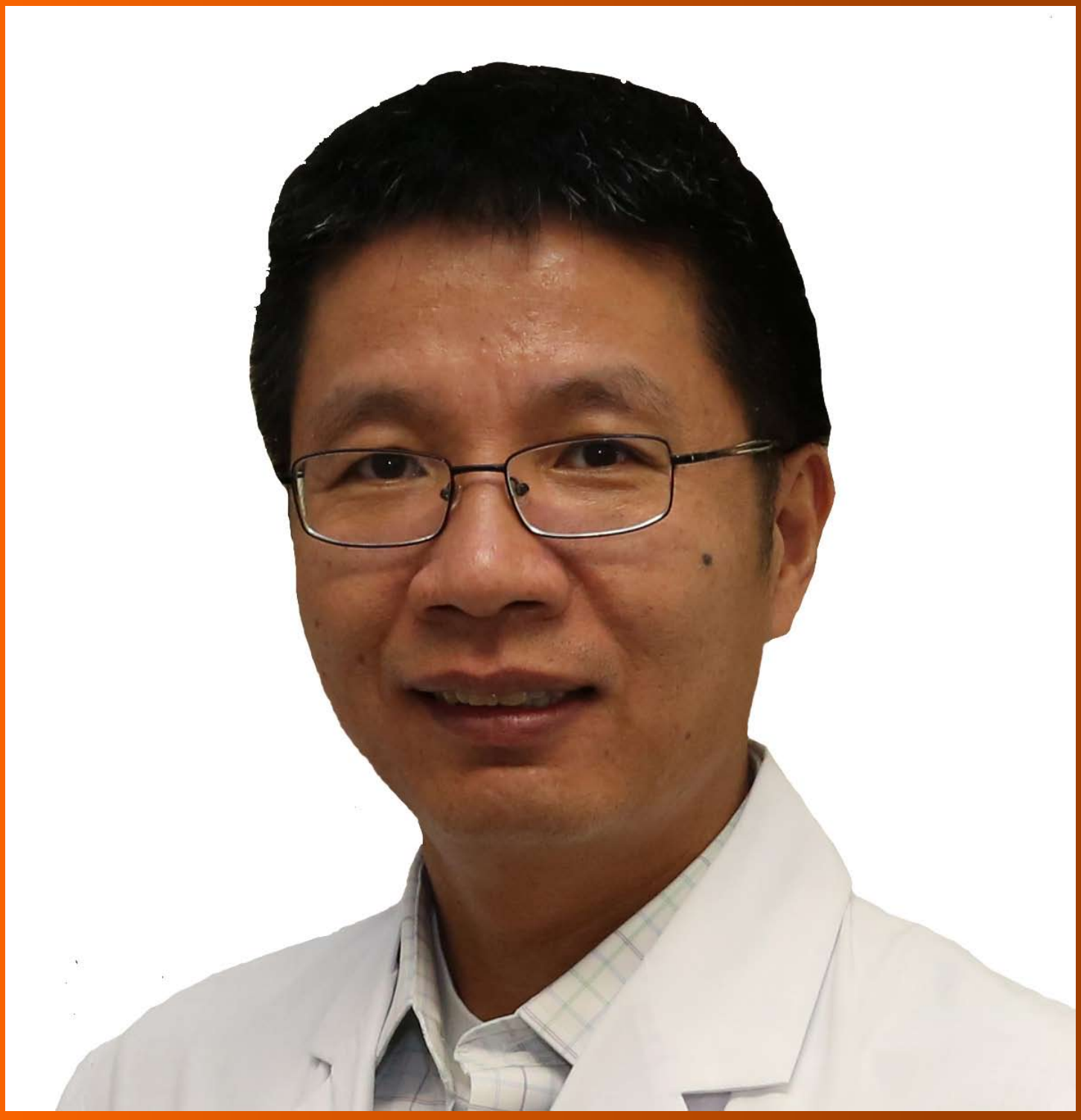

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MINIREVIEWS

From traditional serrated adenoma to tubulovillous adenoma and beyond

Sangeetha N Kalimuthu, Adeline Chelliah, Runjan Chetty

Sangeetha N Kalimuthu, Adeline Chelliah, Runjan Chetty, Department of Pathology, Laboratory Medicine Program, University Health Network and University of Toronto, Toronto M5G 2C4, Canada

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Correspondence to: Runjan Chetty, MD, Professor, Department of Pathology, Laboratory Medicine Program, University Health Network and University of Toronto, 200 Elizabeth Street, 11th Floor, Eaton Wing, Toronto M5G 2C4, Canada. runjan.chetty@gmail.com
Telephone: +1-416-3405319
Fax: +1-416-3405517

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Abstract

It is well established that colorectal cancer develops from a series of precursor epithelial polyps, including tubular adenomas, villous/tubulovillous adenomas (VA/TVA), sessile serrated adenomas (SSA) and traditional serrated adenomas (TSA). Of these, TSAs are least common and account for only 5% of all serrated polyps. TSAs are characterised by the presence of a "pinecone-like" architecture, granular eosinophilic cytoplasm, luminal serrations, ectopic crypt foci (ECF) and elongated, pencillate nuclei. However, the distinct slit-like luminal serrations, reminiscent of small bowel mucosa, appear to be the most unique and reproducible feature to distinguish TSAs from other polyps. There is a contention that TSAs are not inherently dysplastic and that the majority do not show cytological atypia. Two types of dysplasia are associated with TSA. Serrated dysplasia is less well recognised and less commonly encountered than adenomatous dysplasia. In addition, it is now becoming increasingly evident that TSAs can be admixed with HP, SSA and VA/TVA. At a genetic level, polyps may switch phenotype as they accumulate genetic changes, evolving from a serrated pathway to a more conventional one, which could be the basis for a spectrum theory starting out with a TSA with serration and ECF evolving into a TSA with conventional dysplasia and, eventually, to a well-developed conventional adenoma. Nevertheless, there is an exigency for future studies to provide further illumination and bridge the gaps in our present understanding.

Key words: Serrated polyps; Traditional serrated adenoma; Tubullovilous adenoma; Serrated pathway; Fusion pathways

Core tip: Traditional serrated adenoma (TSA) is the least common type of the serrated polyps and is characterized by a constellation of distinct cytomorphological features. TSAs are thought to be precursors to the biologically aggressive, *BRAF* mutated, microsatellite stable,

colorectal cancer. It is becoming increasingly evident that TSAs can co-exist with other serrated polyps including hyperplastic polyps and sessile serrated adenomas. In addition, TSAs may also be seen with adenomatous polyps. In this review, we wish to highlight the issues around nomenclature, diagnostic criteria, coexistence with other polyp types, the occurrence of dysplasia and molecular pathways involved in the neoplastic progression of TSAs.

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INTRODUCTION

It is well established that colorectal cancer (CRC) develops from a series of precursor epithelial polyps[1-5], which include conventional adenomas, incorporating tubular adenomas and villous/tubulovillous adenomas (VA/TVA) and serrated polyps, incorporating hyperplastic polyps (HP), sessile serrated adenomas (SSA) and traditional serrated adenomas (TSA)[1,2,4,6,7]. CRC is known to develop through three putative molecular pathways with the conventional adenoma-carcinoma sequence (chromosomal instability pathway), the mismatch repair and serrated pathways, accounting for the molecular pathogenesis of most CRCs[2,4]. VA/TVAs are thought to be the advanced precursors in the "adenoma-carcinoma" pathway[2]. Obversely, CRCs arising from serrated polyps (which can be visible at the edge or intimately associated with the invasive tumour), are thought to be portentous of the "serrated pathway"[1,4,8-10]. All three serrated polyps stay true to their epithet by characteristically demonstrating luminal serrations. Of these, TSAs are the least common and account for only 5% of all serrated polyps[1].

NOMENCLATURE AND CLINICOPATHOLOGICAL CRITERIA

The historical provenance and journey taken to recognise TSAs in their present guise has been an interesting one. TSAs were first recognised by Longacre and Fenoglio-Preiser[11,12] and were grouped together under the broad term of "serrated adenomas", as these polyps were thought to be conventional adenomas with a serrated luminal profile. Torlakovic *et al*[13] further refined this definition by appending the term "traditional" to the appellation, specifically to distinguish TSAs from SSAs and later highlighted several distinct morphological features specific to TSAs[14].

TSAs are equally distributed between the genders and usually present in the sixth to seventh decade of life[11]. They range from 9-14 mm in maximum dimension and endoscopically have a pinecone-like appearance or may exhibit a fernlike/stellate pit pattern on chromoendoscopy[11].

TSAs can be both sessile and pedunculated, the former being more common in the more proximal lesions[11]. Histologically, TSAs are exemplified by a constellation of characteristic cytomorphological features, which include a tubulovillous, "pinecone-like" architecture, striking granular eosinophilic cytoplasm, presence of ectopic crypt foci (ECF), distinct luminal serrations, elongated, pencillate nuclei with evenly dispersed chromatin and small inconspicuous nucleoli and haphazardly distributed goblet cells (Figure 1)[2,4,6,9,10,14]. Of these lineaments, the distinct slit-like luminal serrations with mushroom/jigsaw puzzle-like broad luminal fronds, reminiscent of small bowel mucosa, appear to be the most unique and reproducible feature to distinguish TSAs from other polyps[6,8,11]. Interestingly, Bettington *et al*[5] have recently described a "serrated" TVA, which occurs more frequently in a proximal location and in essence, morphologically resembles a conventional TVA but at least > 50% of the polyp displays prominent serrations. The authors argue that this represents a distinct entity, with more frequent *KRAS* mutations and CpG island methylation; however, we surmise that the "undulating" or "maze-like" serrations described may merely represent a morphological spectrum seen within TVAs and could possibly be secondary to mechanical compression due to luminal spatial constriction. This latter conjecture could possibly elucidate why this particular type of serration may, at least focally, be observed in larger polyps harbouring a villous configuration, albeit almost never seen in TSAs. Nevertheless, it is important to distinguish serrated TVA from TSA, particularly in the scenario when TSAs co-exist with conventional TVAs[6].

ECF have been defined as abnormal development of crypts, secondary to inactivating mutations in the bone morphogenetic protein 4 signalling pathway, causing loss of orientation towards the muscularis mucosae resulting in these short disorientated abortive crypts that fail to reach the muscularis mucosae (Figure 1)[2,6,14]. ECF were previously touted to be a prerequisite for the diagnosis of TSA[14]. However, these "maelstrom-like" or whorled clusters may not always be seen in TSAs[2,6,8,15], particularly in smaller lesions (< 10 mm) and have also been documented in VA/TVAs (34%)[2], albeit to a lesser frequency than observed in TSAs.

TSA WITH OTHER COEXISTENT POLYPS

When most of the aforementioned hallmark features are represented, a diagnosis TSA can be made with minimal difficulty. However, it is becoming increasingly evident that TSAs can be admixed with HP, SSA and VA/TVA[1,2,6,16,17]. The documented rate of co-existent HP/SSA and VA/TVA with TSA range from 31%-52%,

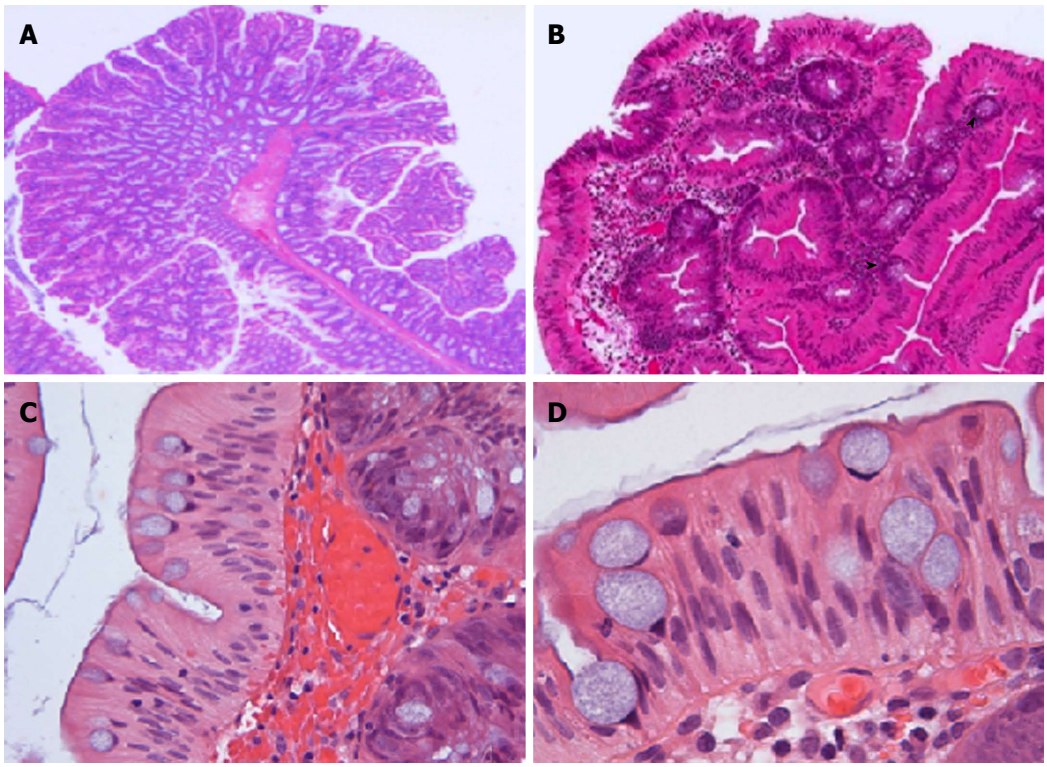

Figure 1 Traditional serrated adenoma. A: Traditional serrated adenoma (TSA) demonstrating an arborizing, "pinecone-like" pattern; × 12.5; B: TSA replete with abortive crypts or ectopic crypt foci (ECF) (arrowhead); × 100; C: Characteristic slit-like luminal serrations with deep clefts and indentations, resulting in mushroom-like or jigsaw puzzle-like appearance, which resemble the apical brush border of small bowel; × 200; D: The epithelial cells have intensely eosinophilic cytoplasm with centrally located palisaded, regular, pencillate nuclei and nuclear grooves. In addition, there are haphazardly distributed goblet cells with apical mucin and basally located nuclei; × 400 (all H and E).

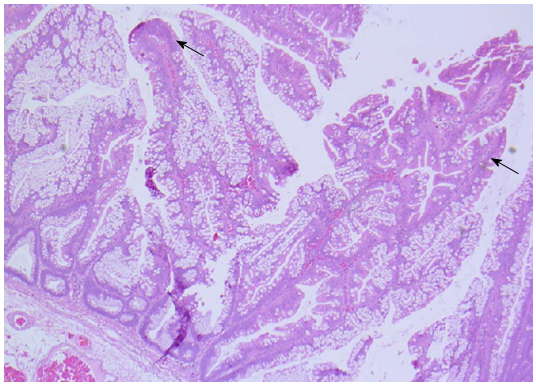

Figure 2 Sessile serrated adenoma with the characteristic dilated crypts. It is a horizontal growth along the muscularis mucosa and deep serration, seamlessly merging with foci of traditional serrated adenomas like areas (arrow); × 100, H and E.

14%-17% and 17%-43%[1,2,15,16], respectively. There is presently sufficient evidence to suggest that a significant proportion of TSAs contain precursor lesions in the form SSAs (Figure 2)[3,4,17], the former being more common of the two. These lesions are often seen intimately associated with the TSA. In contrast, the adenomatous polyps are sharply delineated from the TSAs and appear separate and morphologically distinct (Figure 3A). It is important not to over-document a co-existent adenomatous component when adenomatous dysplastic glands occur within a TSA (Figure 3). It is helpful to recognise that dysplastic glands in TSAs more or less retain the characteristic serrations and will be more replete with ECFs than expected in VA/TVAs.

TSA AND DYSPLASIA

The subject of dysplasia in TSA has long been a contentious one. Historically, TSAs were considered to be inherently dysplastic, owing to the close cytological resemblance to tubular adenomas or TVA[12]. However, this axiom has since been challenged and there is an alternate view proposed[8,10,11,15]. TSAs are unquestionably neoplastic; however, the absence of overt cytological atypia, infrequent or absent mitoses, low Ki-67 proliferation index, consistent B-catenin and p53 negativity, and retention of p16 staining, suggest TSAs are not intrinsically dysplastic[6,10,11,15]. Instead, the cells of TSAs may represent metaplastic or senescent cells[10,15]. It is noteworthy that there are two forms of dysplasia that can occur in TSAs and indeed in the other two serrated polyps[4,9,10,17]. The first is the well-accepted conventional adenomatous dysplasia, which can be readily recognised with minimal difficulty. The second, less well recognised and controversial, is serrated dysplasia. Serrated dysplasia manifests secondary to activation of the serrated pathway, which is initiated by *BRAF* mutations[4,7,10,11,18]. Similar to

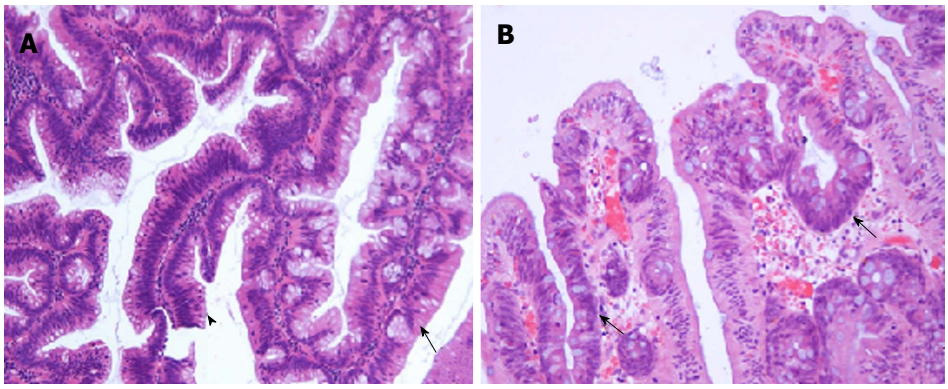

Figure 3 Traditional serrated adenoma and dysplasia. A: Traditional serrated adenoma (TSA) (arrow), sharply demarcated form more a more conventional tubulovillous adenoma (TVA) (arrowhead); × 100; B: TSA with conventional dysplasia with some preservation of the characteristic architecture; × 200 (both H and E).

adenomatous dysplasia, this form of can be graded as low grade and high grade based on both cytological and architectural features. Low grade serrated dysplasia can be subtle and is characterised by ovoid enlarged nuclei, vesicular dispersed chromatin with low mitotic activity. In addition, scattered dystrophic goblet cells may also be observed[6,1,18]. In contrast, high grade dysplasia is readily recognisable as a result of severe cytological and architectural atypia. Currently, the biological significance of low grade serrated dysplasia is poorly understood. As such, in practice, it is recommended that only high grade serrated dysplasia be reported.

While the majority of the adenomatous polyps encountered may only display a single phenotype, in our experience, closer scrutiny often reveals isolated TSA-like glands or SSA/HP like areas. However, from a practical point of view, the sensible approach would be to name the polyp after the most dominant histological type, followed by any secondary or tertiary component identified with an accompanying comment as to the presence or absence of dysplasia.

MOLECULAR PATHWAYS

At a molecular level, the morphological alteration in phenotype may possibly be secondary to the transition from the serrated pathway to a more conventional one. For example, when conventional dysplasia ensues in a TSA, it is possible that the Wnt signalling pathway typically associated with chromosomal instability alters its morphology[4]. Hence, the classic TSA with serrations and ECF, evolves into a TSA with conventional dysplasia and eventually, focally or entirely, resembling a conventional well-differentiated adenoma. This presupposes that molecular aberrations result in consistent morphological appearances. Jass *et al*[3] was the first to propose the theory where separate to the adenoma-carcinoma and serrated pathway, there may be "fusion" pathways that combine mechanisms associated with both adenomatous and serrated polyps[3,4]. However, further studies are required to consolidate this assertion.

CONCLUSION

Overall, it stands to reason that there is a considerable morphological overlap between different polyp types, albeit the molecular basis to which remains to be elucidated. Although conjectural, recent evidence raises the important question as to whether these polyps truly represent separate entities or are they merely manifestations at different stages of a morphological and/or molecular continuum. Nevertheless, there is an exigency for future studies to provide further illumination and bridge the gaps in our present understanding.

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Role of circulating free DNA in colorectal cancer

Alexios Matikas, Alexandra Voutsina, Maria Trypaki, Vassilis Georgoulias

Alexios Matikas, Alexandra Voutsina, Maria Trypaki, Vassilis Georgoulias, Laboratory of Tumor Cell Biology, School of Medicine, University of Crete, Voutes, Heraklion, 71110 Crete, Greece

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Correspondence to: Alexios Matikas, MD, Msc, Laboratory of Tumor Cell Biology, School of Medicine, University of Crete, Voutes, PO Box 1352, Heraklion, 71110 Crete, Greece. georgsec@med.uoc.gr
Telephone: +30-2810-392783
Fax: +30-2810-543601

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Abstract

The gradual elucidation of the underlying biology of colorectal cancer has provided new insights and therapeutic options for patients with metastatic disease which are selected according to predictive biomarkers. This precision medicine paradigm, however, is incomplete since not all eligible patients respond to these agents and prognostic stratification is largely based on clinicopathologic variants. Importantly, no robust data exist to help properly select patients with localized disease at high risk for recurrence and most likely to benefit from adjuvant chemotherapy. There is a rapidly expanding body of literature regarding the role of the qualitative and quantitative analysis of circulating free DNA in various neoplasms, which consistently outperforms traditional tumor markers both as a predictive and as a prognostic marker. Several lines of evidence suggest that circulating free DNA may exhibit a complementary role to existing modalities for the early diagnosis of colorectal cancer, the selection of patients for adjuvant chemotherapy, for the follow-up of treated patients, for the selection of treatment for advanced disease and the assessment of response and for determining the prognosis of patients. These data, which are reviewed here, illustrate the important role that circulating biomarkers may soon have at the daily clinical practice.

Key words: Cell-free DNA; Circulating tumor DNA; Colorectal cancer; Biomarker; KRAS

Core tip: Published studies clearly indicate that cell-free DNA levels and the detection of specific molecular events in the plasma of colorectal cancer patients is a relevant prognostic and predictive biomarker, with clinically meaningful value at various disease settings such as asymptomatic screening, follow-up after curative surgery and metastatic disease. Further randomized studies are needed before these techniques are implemented at the daily practice.

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INTRODUCTION

Globally, colorectal cancer (CRC) is the third most commonly diagnosed cancer in males and the second in females; there is a significant regional variation in incidence and mortality rates in Western countries, especially the United States, where both are decreasing as a result of the widespread adoption of effective screening policies and of the evolution of treatment strategies at the adjuvant setting. Approximately 8% of cancer deaths are caused by CRC[1,2]. Twenty percent of newly diagnosed patients have *de novo* clinically overt metastases; moreover, 10% of patients diagnosed with local and 30% with regional disease will eventually relapse, most commonly with disseminated disease[3]. These patients presumably already harbor occult micrometastases, thus identifying them and administering systemic treatment following local excision may improve their chance for cure. Moreover, despite significant advances in the understanding of underlying molecular mechanisms and in the development and regulatory approval of several active agents during the past 15 years, 5-year survival rates of patients with metastatic CRC (mCRC) remain poor at 13%[3], with the majority of these patients receiving palliative systemic treatment without a curative intent. Thus, it is clear that earlier diagnosis when interventions may be curable and also better predictive and prognostic biomarkers both for localized and advanced disease are highly needed.

Liquid biopsy is a minimally invasive process based on a simple venipuncture that potentially addresses several issues, since it can be safely implemented on a wide scale basis and can be repeated with minimal risks for the patient. Moreover, liquid biopsy may illustrate the molecular diversity of the underlying disease process and serial testing facilitates the monitoring of its spatial and temporal genomic evolution and at the same time it circumvents the need for re-biopsy, which is invasive, cumbersome and not always feasible[4]. Moreover, re-biopsy is subject to sampling bias and it may not be representative of the intratumoral heterogeneity. These biomarkers may be protein-based, such as cancer antigens [carcinoembryonic antigen (CEA)], cell-based, such as circulating tumor cells (CTC) and disseminated tumor cells and nucleic acid-based, such as circulating cell-free DNA (cfDNA) and micro RNAs. CEA has been the only circulating biomarker in clinical use for decades, but its usefulness is limited by suboptimal sensitivity and specificity[5].

CIRCULATING cfDNA

cfDNA may originate from normal or from tumor cells and it can be detected in healthy subjects, with increased levels noted in benign conditions such as inflammatory processes and infections[6]. Necrotic and apoptotic cells may release DNA fragments passively, depending on the tumor burden, its growth kinetics and the effects of antineoplastic treatment, but it is also believed that cfDNA may be actively shed by tumor cells with the goal to transform cells in distant sites[7]. Finally, CTCs and micrometastases may also be the source of cfDNA, along with the primary tumor.

Several technical challenges hamper the ability to standardize the identification and measurement of cfDNA in oncology patients. First of all, the low concentration of highly fragmented DNA molecules renders their identification, amplification and quantification rather challenging[8]. Several DNA extraction methodologies have been developed with no one appearing to clearly improve yields and pre-analytical sample processing and storage could potentially influence results. Moreover, the abundance of available methodologies such as digital polymerase chain reaction (PCR), real-time quantitative PCR (qPCR) and emerging next-generation sequencing technologies result in a lack of comparability between results reported in various translational and clinical studies[9,10]. Despite these challenges, an exponentially increasing body of literature has clearly demonstrated the promise that the measurement of cfDNA holds in various clinical settings and in multiple different neoplasms and advances in technology aim to tackle both the problems of detecting diluted tumor DNA and determining its origin based on the presence of known aberrations found on the primary tumor.

EARLY DIAGNOSIS OF COLORECTAL CANCER

Screening for CRC has been consistently shown to reduce disease specific mortality[11]. An abundance of screening modalities is available and recommended by clinical practice guidelines, which implies that no one is clearly superior to the others since no randomized comparisons have been performed[11,12]. Colonoscopy is regarded as the preferred technique[13]. However, it is costly and invasive. Thus, enriching the population that undergoes colonoscopy with subjects at the highest risk for the development of CRC with a minimally invasive selection procedure is a matter of active research.

A large number of studies, reviewed elsewhere[14], have evaluated the efficacy as screening tools of the detection of several molecular events, such as kirsten rat sarcoma viral oncogene homolog (KRAS), adenomatosis polyposis coli, TP53 and mismatch repair genes (*MMR*) mutations, DNA methylation and miRNA signatures in body fluids, mainly stool but also plasma and serum. In summary, the reported sensitivity and specificity rates vary widely, owing to the small quantity of hyperfragmented DNA, often of low quality, retrieved from body fluids (especially stool) and the different

techniques and biomarkers tested. Regarding plasma cfDNA, preliminary results are promising. In a high risk population with positive fecal occult blood test that subsequently underwent colonoscopy, Perrone *et al*[15] demonstrated that the quantification of cfDNA by qPCR was predictive for CRC but not premalignant lesions (area under curve, 0.709; 95%CI: 0.508-0.909). This important finding clearly illustrates that cfDNA can have a complementary role to traditional screening modalities for CRC. In the same study, the detection rate of KRAS mutations in the plasma by mutant-enriched PCR was low at 3%, compared to tissue-based analysis (45%). However, KRAS mutations can also be detected in patients with inflammatory bowel disease, complicating the interpretation of its significance[16]. Significant barriers to the implementation of cfDNA-based strategies include the relatively low sensitivity especially for premalignant lesions and the probability of over-diagnosis.

MONITORING MINIMAL RESIDUAL DISEASE

Following curative surgery for localized CRC, approximately 50% of stage Ⅲ patients according to the American Joint Committee on Cancer (node-positive disease) and 20% of stage Ⅱ patients (T3N0 and T4N0) are expected to experience disease relapse without adjuvant chemotherapy, possibly due to the presence of occult micrometastases. Therefore, identifying these high risk patients could optimize adjuvant treatment strategies. The benefit derived from chemotherapy is well established for stage Ⅲ patients, with the results of large, well-conducted randomized trials demonstrating a benefit for overall survival (OS) for patients treated with the combination of a fluoropyrimidine (5-fluorouracil or capecitabine) and oxaliplatin (FOLFOX and XELOX, respectively)[17,18]. The management of stage Ⅱ patients is much more controversial, as clinical trials and meta-analyses indicate that the absolute risk reduction is marginal and sometimes non-significant[19-21]. Clinical practice guidelines recommend the use of clinic-pathological risk factors for the selection of eligible patients for adjuvant chemotherapy, such as T4 stage, perforation, obstruction, number of lymph nodes resected, presence of lymphovascular or perineural invasion, poor grade, preoperative CEA levels and positive or indeterminate margins[22-24]. Additionally, molecular markers such as the presence of microsatellite instability[25] and gene signatures[26] have also been shown to have prognostic and/or predictive value. These data clearly underscore that robust decision making tools are needed for the selection of patients that will enjoy improved outcomes from additional chemotherapy, thus sparing from its toxic effects those not likely to benefit. Consequently, cfDNA has been evaluated in this setting. Reinert *et al*[27] recently showed that using droplet digital PCR-based (ddPCR) personalized assays, the quantification of plasma cfDNA had almost 100% sensitivity and specificity for the prediction of relapse after surgery, with a mean lead time of 10 mo. Furthermore, the value of cfDNA measurement specifically in stage Ⅱ CRC patients is being prospectively evaluated, with preliminary results showing that 7.7% of patients who had detectable cfDNA after curative surgery had higher relapse rates, 5/6 patients with detectable and 5/72 of those with undetectable cfDNA[28]. The selection of the proper mutation markers to be monitored in cfDNA is as yet unresolved. Sato *et al*[29] monitored preoperative and postoperative cfDNA levels based on a panel of 50 genes, using ddPCR; only markers with an allele frequency above 0.1% in plasma DNA correlated with the clinical course. Interestingly, cfDNA has also been shown to be useful in the early detection of relapse after metastasectomy of liver metastases, significantly outperforming both CEA and imaging in one study[30].

PREDICTION OF RESPONSE TO TREATMENT

The demonstration of the efficacy of monoclonal antibodies (moAbs) targeting the epidermal growth factor receptor (EGFR), such as cetuximab and panitumumab, in specific molecular subtypes of mCRC, marked a significant breakthrough towards the delivery of precision medicine. V-Ki-ras2 KRAS has a critical role in EGFR signaling transduction. Activating KRAS mutations at exon 2 are detected in approximately 40%-45% of patients with CRC and have been shown to confer resistance to treatment with cetuximab[31,32] and panitumumab[33]. Moreover, less common KRAS mutations at exons 3 and 4 and NRAS mutations at exons 2, 3, 4 identified at a further 17% of patients have been shown to also correlate with resistance to anti-EGFR moAbs[34]. On the other hand, mutations at the B-Raf proto-oncogene, serine/threonine kinase (BRAF), which is further downstream at the mitogen-activated protein kinase (MAPK) pathway have been shown to have significant prognostic, but not predictive value as a marker of poor response to anti-EGFR antibodies when combined with chemotherapy, although evidence for the latter is not compelling due to the small number of patients and low statistical power of these analyses[35,36]. To further complicate matters regarding the role of BRAF mutations, several lines of evidence suggest that their presence is a marker of resistance to monotherapy with anti-EGFR moAbs[37-39].

Availability of adequate tissue is rarely a problem in CRC patients. Additionally, there is a high rate of concordance between the primary tumor and metastases regarding the mutational status of mCRC but, importantly, approximately 10% of patients with KRAS wild type (WT) primary tumors have KRAS mutated metastases and *vice versa*[40]. Qualitative analysis of cfDNA for the presence of activating mutations is an

emerging method which has been consistently shown to closely correlate with the primary tumor status. For example, Morgan *et al*[41] utilized a commercial PCR kit and demonstrated that the detection of KRAS mutations in cfDNA is highly concordant with their presence at the primary tumor and they could also be detected in the plasma of a patient with KRAS WT primary. Accordingly, Thierry *et al*[42] showed in a prospectively evaluated patient cohort that qPCR-based detection of KRAS and BRAF mutations in mCRC patients is exquisitely sensitive and specific when using the primary tumor status as a reference standard, results that have been confirmed by others[30]. Taken together, these data clearly imply that the detection of predictive molecular events in mCRC patients is an excellent surrogate for their presence at the primary tumor and could be used in cases where archival tumor is not available or when the acquisition of fresh tissue is not feasible.

MONITORING RESPONSE TO THERAPY

The quantitative measurement of a known aberration in the plasma may be used for disease monitoring of mCRC patients while under treatment and data show that cfDNA levels robustly correlate with tumor burden and response to treatment, raising the possibility of its use at the near future as an adjunct to anatomical imaging. Several investigators have established the correlation between tumor burden, cfDNA and levels of specific mutations such as KRAS in circulation[42-44]. Moreover, high levels of cfDNA were shown to be predictive for diminished disease control rates when mCRC patients were treated with irinotecan and cetuximab in a study by Spindler *et al*[43]. In a prospective trial of mCRC patients undergoing first-line chemotherapy, a 10-fold or higher reduction in circulating tumor DNA (ctDNA) before cycle 2 correlated well with CT imaging at 8-10 wk while lesser degrees of reduction were associated with a trend for improved progression free survival (PFS)[45]. Although the quantification of cfDNA levels and their temporal changes seem appealing for clinical use, two issues need to be considered: First of all, benign conditions such as infections may also lead to raised cfDNA levels. Also, the genomic evolution of the tumor could potentially lead to alterations in cfDNA levels regardless of tumor burden. Until more specific and sensitive methods that measure ctDNA are available, it is prudent that cfDNA levels are used in combination with imaging scans for response assessment.

DETECTION OF RESISTANCE

Despite appropriate patient selection according to molecular testing, approximately 10% of treatment naïve patients experience disease progression as best response when receiving first line treatment with a chemotherapy doublet and an anti-EGFR antibody[46]; importantly, virtually all patients will eventually develop disease progression while receiving such treatment. The resistance mechanisms of mCRC to anti-EGFR moAbs can be broadly categorized in three categories and it should be mentioned that there is significant overlapping between primary and secondary resistance, with a few notable exceptions: (1) events that disrupt the binding of cetuximab or panitumumab at the EGFR. These events may be point mutations, with the best characterized being the S492R mutation which interferes with the binding of cetuximab but not panitumumab[47], a decrease of EGFR copy number or differential expression of the EGFR ligands epiregulin and amphiregulin[48]; (2) activation of downstream kinases, effectively bypassing the inhibition of EGFR. The best described events include the KRAS, NRAS and BRAF mutations whose role at the primary resistance was previously described. Although less common, *KRAS* gene amplification has also been implicated in the development of resistance to cetuximab and panitumumab[49]; and (3) activation of parallel, bypassing pathways. The most commonly described mechanisms are phosphatidylinositol-4,5-bisphosphate 3-kinase catalytic subunit alpha exon 20 mutations in approximately 10%-15% of patients and phosphatase and tensin homolog (PTEN) mutations in 18%, both leading to activation of the PI3K/AKT/mTOR pathway[39,50]. However, since these mutations frequently coexist with other resistance mechanisms such as KRAS mutations, it is difficult to establish a potentially direct causative role. Other genomic events that have been implicated in the development of secondary resistance are HER2 amplification[51], IGF-1R activation[52] and MET amplification[53].

It is clear that CRC exhibits significant spatial and temporal heterogeneity while under the selective pressure of treatment, which is further complicated by the extensive crosstalk, shared downstream pathways and bypass signaling that is activated during treatment with anti-EGFR moAbs which allows pre-existing resistant clones to emerge. The early recognition of these molecular mechanisms, before disease progression is clinically or radiologically apparent, may offer a better chance at intercepting them, thus improving patient outcomes.

The best studied in cfDNA mechanism of acquired resistance is the emergence of KRAS mutations, which has been shown to occur while under treatment both with cetuximab[54] and panitumumab[55]. Notably, in a series of CRC patients receiving treatment it was shown that KRAS mutations developed in 38% of patients previously responding to anti-EGFR moAbs, 96% had newly acquired activation of the MAPK pathway and 70 new somatic mutations were described in total[56]. Interestingly, in a series of 108 mCRC patients pretreated with a fluoropyrimidine, irinotecan and oxaliplatin, who received irinotecan and cetuximab, Spindler *et al*[57] demonstrated that the emergence of detectable KRAS mutations in the plasma may precede

radiological progression and that patients with a KRAS mutant primary but no detectable mutations in the plasma could benefit from treatment despite previous exposure to and progression after irinotecan.

Apart from KRAS mutations, other molecular events that emerge under the selective pressure of anti-EGFR treatment and that drive resistance to these agents have been detected in cfDNA, such as EGFR mutations[58] and MET amplification[53]. The relative importance of each specific aberration, in light of the frequent co-existence of several mechanisms in a single patient[59] needs to be elucidated in further studies.

CELL-FREE DNA AS A PROGNOSTIC MARKER

The prediction of survival in mCRC patients relies heavily on clinic-pathologic characteristics, such as hepatic tumor burden, node positive primary, CEA levels, microsatellite stability status, BRAF mutation status, resectability of metastatic disease and tumor grade[60]. Objective and reproducible biomarkers are needed in order to optimize risk stratification and guide treatment decisions. The prognostic capacity of quantitative and qualitative cfDNA characteristics have been investigated in several studies. cfDNA levels were indeed shown to correlate with survival in mCRC[56], including at the second line setting where increased cfDNA levels predicted shorter PFS and OS compared to lower levels, with a hazard ratio (HR) of 1.4 (95%CI: 1.1-1.7, P = 0.03) for PFS and 1.6 (95%CI: 1.3-2.0, P < 0.0001) for OS for each quartile of increase[61]. Qualitative characteristics, such as methylated cfDNA levels have also been shown to independently predict OS in mCRC[62]. In the largest published prospective mCRC patient cohort (n = 97), El Messaoudi *et al*[63] used qPCR and showed that cfDNA levels, higher specific mutation loads and the level of cfDNA fragmentation are strong prognostic factors; cfDNA levels were independent prognostic factors for the entire patient cohort and the level of fragmentation only for the KRAS/BRAF mutated subset. Specifically, a difference in OS of 10 mo was reported between the groups of high *vs* low cfDNA levels (18.07 mo *vs* 28.5 mo respectively, P = 0.0087)[63]. Finally, Spindler *et al*[64] compared the prognostic value of the detection of KRAS mutations in the plasma compared to the primary tumor with the use of qPCR, with the former being an independent predictor for OS (HR = 2.98, 95%CI: 1.53-5.80, P = 0.001) and PFS (HR = 2.84, 95%CI: 1.46-5.53, P = 0.002), whereas the latter had no correlation with outcomes, which underscores the value of cfDNA qualitative testing.

DISCUSSION

There is enormous interest for the discovery, development, clinical evaluation and standardization of circulating biomarkers in oncology, since liquid biopsy offers the possibility of real-time monitoring of the disease trajectory. Due to the absence of large scale comparisons of the relative efficacy of cfDNA and CTCs and the lack of standardization of clinical assays, no clear recommendations can be made on which is the superior biomarker and published literature suggests that they may be complementary[65,66]. For example, CTCs have been shown to be useful in determining the level of heterogeneity of the disease, with significant differences compared to the primary tumor demonstrated in single cell whole genome analysis. Moreover, the phenotypic and genotypic characterization of CTCs could be a powerful tool aiding treatment planning and determining the likelihood of drug resistance[67]. However, the large number of CTC capture and enrichment techniques, which are based on antibody selection or on the physical properties of CTCs and the often times low quantity and quality of DNA extracted from these rare cells represent significant drawbacks[68].

Contrary, cfDNA exhibits several important advantages: Its extraction is less cumbersome compared to CTCs, but the preanalytical process is equally non-standardized. Also, multiple studies across various neoplasms have shown that its qualitative and quantitative measurement is representative of the overall tumor burden and of the mutational load of the disease and its heterogeneity. Therefore, its future potential role as a complement in asymptomatic screening and disease staging, as a tool for disease monitoring even without the use of anatomic imaging, as a prognostic marker and for the long term follow-up of disease free patients with CRC is exciting[69]. Nevertheless, the aforementioned lack of standardization is a significant obstacle for the commercialization and widespread adoption of cfDNA in oncology. Moreover, cfDNA, in contrast with CTCs, does not provide information regarding RNA and protein profiling of the tumor. However, sensitivity may be improved since cfDNA has been detected both in patients with and without detectable CTCs, but CTCs were not detected in the absence of cfDNA[56]. These observations clearly hint towards a combinatory approach to circulating biomarkers.

It is conceivable that in the near future serial cfDNA testing will become a component of routine clinical practice regarding the management of CRC. Its already established prognostic power may be integrated in novel staging schemes and its predictive capacity may influence treatment decisions. Importantly, its use may spare patients from unnecessary toxicity caused by ineffective treatments. It is imperative, however, that cost-effectiveness analyses be conducted since these costly techniques require specific equipment and are often labor-intensive.

CONCLUSION

cfDNA has already shown promise in CRC in multiple

clinical settings. Its prospective evaluation in randomized trials is of paramount importance before it can be considered as standard practice and cost-effectiveness analyses are also needed. Until then, translational studies continue to underscore its clinical utility and offer insights on the continuously evolving understanding of the disease complexity.

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ORIGINAL ARTICLE

Retrospective Study

Signet ring colorectal carcinoma: Do we need to improve the treatment algorithm?

Anup Sunil Tamhankar, Parag Ingle, Reena Engineer, Munita Bal, Vikas Ostwal, Avanish Saklani

Anup Sunil Tamhankar, Parag Ingle, Department of Surgical Oncology, Tata Memorial Centre, Mumbai, Maharashtra 400012, India

Reena Engineer, Department of Radiotherapy, Tata Memorial Centre, Mumbai, Maharashtra 400012, India

Munita Bal, Department of Surgical Pathology, Tata Memorial Centre, Mumbai, Maharashtra 400012, India

Vikas Ostwal, Department of Medical Oncology, Tata Memorial Centre, Mumbai, Maharashtra 400012, India

Avanish Saklani, Department of Gastro-Intestinal Surgery, Tata Memorial Centre, Mumbai, Maharashtra 400012, India

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Correspondence to: Dr. Avanish Saklani, MS, FRCS, Associate Professor, Department of Gastro-Intestinal Surgery, Tata Memorial Centre, Mumbai, Maharashtra 400012, India. asaklani@hotmail.com
Telephone: +91-996-9506719
Fax: +91-222-4177000

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Abstract

AIM

To elaborate about this peculiar variant from a tertiary cancer center from India.

METHODS

It's a retrospective study (2011-2014) of all patients diagnosed with signet ring colo-rectal cancer (SRCC). Various clinico-pathological variables were studied.

RESULTS

One hundred and seventy consecutive patients with SRCC were diagnosed (11.4% of all colorectal cancers). Median Age of the cohort was 41 years. Most common location was recto-sigmoid area (54.7%). Majority patients presented in stage III and IV (91.2%). Most of the stage IV patients had isolated peritoneal metastases (86.5%). Colonic tumors had higher incidence of peritoneal metastases (91.8% *vs* 83.3%) as well as isolated peritoneal recurrences (37.5% *vs* 16.7%) than rectal primaries. Thirty-seven point five percent of patients recurred after curative surgery. Amongst them 63.63% patients had isolated peritoneal recurrences. Circumferential resection margin (CRM) was involved in 17.9% patients. Median relapse free survival (RFS) and overall

survival (OS) of the cohort were 14.9 and 18.13 mo respectively. CRM involvement, colonic primary were associated with poorer RFS and OS.

CONCLUSION
SRCC has predilection for peritoneal dissemination. More aggressive and/or extended chemotherapy schedules as well as prophylactic hyperthermic intra-peritoneal chemotherapy at the time of primary surgery may be attempted in these patients.

Key words: Colorectal cancer; Signet ring cell carcinoma; Peritoneal metastases; Hyperthermic intra-peritoneal chemotherapy

Core tip: The incidence of Signet Ring Colo-Rectal Cancer appears to be higher in Indian subcontinent than the world literature. It has predilection for peritoneal lining. It affects younger age group. Majority cases present in stage III and IV. Recto-sigmoid region is affected commonly. The most common metastatic site and site of recurrence is peritoneal cavity. Probably it should be treated with a different protocol than the conventional adenocarcinoma with focus on aggressive peritoneal cytoreductions and hyperthermic intra-operative intraperitoneal chemotherapy (HIPEC). Further research is needed to evaluate molecular biology of this variant and utility of prophylactic HIPEC during curative surgery.

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INTRODUCTION

Colorectal cancer (CRC) is one of the most common cancers worldwide[1]. There are three subtypes described in the literature based on the amount and location of mucin in the tumor. These are conventional adenocarcinoma (AC), mucinous carcinoma (MC) and signet ring cell carcinoma (SRCC)[2,3]. SRCC constitutes 1% of all colorectal carcinomas[4-9]. It is an aggressive variant which affects younger population and has poorer prognosis[5]. The literature explaining the biology as well as the optimum treatment algorithm of this particular variant is scarce due to its low incidence. So we look into the incidence, demographics, clinico-radiological presentation and outcome of treatment of this peculiar variant from a tertiary cancer centre from India (Tata Memorial Centre, Mumbai).

MATERIALS AND METHODS

All patients diagnosed with colorectal carcinoma from 1st January 2011 to 31st December 2013, registered under the Department of Gastro-intestinal Oncology services, Tata Memorial Centre, were included. The data was collected retrospectively from Electronic database as well as case files from Department of Surgical Oncology. The histopathology specimens of all these patients were reviewed at Department of Surgical pathology, Tata Memorial Centre. Signet ring cell colorectal cancers were defined as per WHO criteria (AC with more than 50% of signet-ring cells). Patients were staged as per AJCC classification (7th edition). Response to neoadjuvant chemoradioatherapy (NACTRT) was assessed as per RECIST criteria. The decision about the same was taken in the multidisciplinary meeting held for every patient. Pathological complete response was defined as absence of viable tumor cells in the primary, the lymph nodes and peri-rectal soft tissue. Circumferential resection margin (CRM) positivity was defined as presence of viable tumor cells at or within 1 mm of it. Follow up data was obtained from electronic medical records and/or telephonic questionnaire. Recurrences were based on biopsy or strong clinico-radiological evidence. Peritoneal metastases or recurrences constituted peritoneal deposits, malignant ascites, omental deposits and ovarian deposits. Relapse free survival (RFS) was assessed from the date of cancer directed surgery to date of recurrence. Overall survival (OS) was measured from the date of diagnosis of malignancy to date of death. SPSS-21 (IBM corporation) was used for the statistical analysis. Categorical variables were compared with χ^2 test. Survival functions were analyzed with Kaplan Meir curves and compared with log rank test.

RESULTS

From 1st January 2011-31st December 2013, 1487 patients with colorectal cancer got registered under the department of Gastrointestinal Services Tata Memorial Centre. Amongst them, signet ring cell carcinoma was diagnosed in 170 consecutive patients (11.4%). Follow up of 18 of 170 patients (10.58%) was inadequate (< 1 mo) (Table 1). Median Age of the cohort was 41 years. Males were affected nearly twice more than females (M: F = 1.8:1). Most tumors were located in the rectum and sigmoid colon (Rectum: 41.2% and Sigmoid: 13.5%). Majority patients presented in stage III (51.8%) and stage IV (39.4%). Most of the stage IV patients had isolated peritoneal metastases (58/67, 86.5%) (Table 2). Curative surgery was feasible only in 51.76% (88/170) patients. Thirty-seven point five percent (33/88) patients recurred after curative surgery. Twenty-one thirty-thirds (63.63%) patients had isolated peritoneal recurrences (Table 3). Most patients had high nodal burden, pN1 being 23.2% (22/95), pN2 being 57.9% (55/95). Amongst node positive patients, 66.3% (53/77)

Table 1 Demographic parameters

Parameter	Statistics
Total No.	170
Sex ratio	
Male	110
Female	60
Age (median), yr	41
Stage, *n* (%)	
II	6 (3.5)
III	88 (51.8)
IV	67 (39.4)
Not available	9 (5.3)
Location, *n* (%)	
Right colon	49 (28.8)
Transverse colon	13 (7.6)
Descending colon	11 (6.5)
Sigmoid colon	23 (13.5)
Rectum	70 (41.2)
Appendix	1 (0.6)
Not available	3 (1.8)

Table 2 Pattern of metastases in stage IV patients

Site of metastases	*n* (%)
Liver	1 (1.5)
Lung	1 (1.5)
Isolated peritoneal	58 (86.5)
Retroperitoneal lymphnodes	2 (3.1)
Others	5 (7.4)

had perinodal extension. The rate of lymph node metastases and lympho-vascular invasion increased progressively with increasing pathological T stage.

Median RFS and OS of the cohort were 14.9 mo and 18.13 mo respectively. OS of peritoneal and non-peritoneal metastases were equivalent (16 mo *vs* 13 mo, $P = 0.729$) (Table 4).

Forty-eight rectal cancers were operated. Data for patients undergoing NACTRT was available for 37 cases only. Pathological complete response was seen in 21.6% (8/37) patients. CRM was involved in 17.9% (7/39) patients (data on CRM was not available for 9 cases). CRM involvement was associated with poorer RFS (15 mo *vs* 37.2 mo, $P = 0.060$) and OS (19.9 mo *vs* 41.5 mo, $P = 0.018$) as compared to patients with uninvolved CRM (Tables 4 and 5).

The location of primary had a significant impact on the clinico-pathological outcome of the patient. As compared to rectal primaries, colonic tumors had higher incidence of peritoneal metastases (83.3% *vs* 91.8%, $P = 0.074$) as well as isolated peritoneal recurrences (16.7% *vs* 37.5%, $P = 0.062$). Colonic primaries were associated with poorer OS than rectal tumors after curative resection (32.298 mo *vs* 40.089 mo, $P = 0.058$) and RFS (24.74 mo *vs* 34.02 mo, $P = 0.048$) (Table 6).

DISCUSSION

CRC is one of the most common cancers worldwide. Worldwide, it leads to 10% and 9.2% of cancers in

Table 3 Pattern of recurrence after curative surgery

Pattern of recurrence	*n* (%)
Locoregional	4 (12.12)
Distant	4 (12.12)
Isolated peritoneal	21 (63.63)
Peritoneal + second primary	2 (6.06)
Local + peritoneal	2 (3.4)

Regional recurrences: Regional lymph node recurrences; Distant recurrences: Non-regional lymph nodal and visceral recurrences.

Table 4 Factors affecting overall survival

Parameter	OS (mo)	Significance
Location (After curative surgery)		
Colon	32.3	0.058
Rectum	40.1	
CRM		
Positive	19.9	0.018
Negative	41.5	
Metastases		
Peritoneal	14.85	0.729
Non-peritoneal	11.14	

CRM: Circumferential resection margin; OS: Overall survival.

males and females respectively. It is a cause of 8% and 9% of cancer related deaths in males and females respectively[1]. Several histological subtypes have been reported[2,3]. It has two different subgroups apart from classical AC. They are classified based on varying amounts of signet-ring cell and/or mucinous component. Signet-ring cell carcinoma (SRCC) is characterized by intra-cytoplasmic mucin which displaces the nucleus aside. MC is characterized by extracellular mucin pools. SRCC or MC (defined as carcinoma with more than 50% of signet-ring cells or mucinous component, respectively as per WHO classification) constitutes approximately 1% or 5%-15% of CRC cases, respectively in the world literature[4-9]. As compared to the world literature, the incidence of SRCC is much higher in our study (11.4% *vs* 1%). The median age of the cohort in our study was also lower than world literature (41 years *vs* 50-55 years)[5,6,10,11]. This could represent either a referral bias being a tertiary cancer centre in India or definite distinct disease biology in the Indian population. Further studies regarding the demographic profile of this particular variant in Indian population are under consideration currently.

The literature is divided about the most common site of colorectal cancer in young population with some indicating proximal colon[12] and others suggesting it to be recto-sigmoid region[13,14]. In our study, rectum and sigmoid colon region was most commonly affected. This may be related to preferential referral of locally advanced rectal cases to our institute. One of the studies has shown that colorectal cancers affecting younger age group (< 40 years) have significantly higher incidence of signet ring cell cancer. Such tumors also affect rectosigmoid area more commonly than rest of the colon in

Table 5 Factors affecting relapse free survival in operated patients

Parameter	RFS (mo)	Significance
CRM		
Positive	15.003	0.060
Negative	37.202	
Location		
Colon	24.74	0.048
Rectum	34.02	

RFS: Relapse free survival; CRM: Circumferential resection margin.

Table 6 Impact of location on outcome

Parameter	Colon	Rectum	Significance
Recurrence after curative resection			
Peritoneal, *n* (%)	15/40 (37.5)	8/48 (16.7)	0.062
Non-peritoneal, *n* (%)	3/40 (7.5)	7/48 (14.6)	
Pattern of Metastases at presentation			
Peritoneal, *n* (%)	45/49 (91.8)	15/18 (83.3)	0.074
Non-peritoneal, *n* (%)	4/49 (9.2)	3/18 (16.7)	
RFS (mo)	24.74	34.02	0.048
Overall Survival (mo)	26.011	30.32	0.062
OS after curative surgery (mo)	32.298	40.089	0.058

RFS: Relapse free survival; OS: Overall survival.

young patients[15].

SRCC has been associated with peculiar genomic changes such as high-degree microsatellite instability (MSI-high) (up to 40%), high-frequency of CpG island methylator phenotype, higher methylation level of long interspersed nucleotide element-1 and frequent BRAF mutation and low COX-2 expression[8,16-20]. Due to high frequency of MSI-H mutations[21] and associated poor prognosis, tumors with signet ring histo-morphology are recommended to be screened for MSI-H mutations as per revised Bethesda guidelines[22]. The serrated adenoma-carcinoma pathway has been proposed for development of these tumors. Terada *et al*[23] found that epithelial membrane antigen was downregulated in colorectal SRCC. Kim *et al*[24] showed that focal loss of epithelial cell adhesion molecule was associated with development of SRCC in colonocytes. These molecular changes may be related to preferential peritoneal spread of this subtype. Currently the studies are under consideration at our institute to assess genomic changes related to this specific phenotype which may be the cause of higher incidence of signet ring colorectal cancer in Indian population than the world literature.

Our study revealed that, though SRCC has an aggressive biology in general, it seems to respond well to NACTRT with pathological complete response rate of 21%. Literature assessing response of SRCC to NACTRT is scarce due to low incidence worldwide. Jayanand *et al*[25] showed that these tumors respond well to RT with high pathological complete response rates. It may be related to their aggressive nature and higher mitotic index. So potentially NACTRT should be included in the treatment protocol of rectal SRCC for improved outcomes.

Patients with SRCC are more likely to present in advanced stages (Stage Ⅲ/Ⅳ) than AC. SRCC patients more often present with metastatic disease and are more likely to develop peritoneal metastases. This may be related to their peculiar molecular origin which is yet to be proven. It is also shown that SRCC metastasizes to the lymph nodes, whereas AC metastasizes primarily to the liver[6,9,11]. Our study also showed similar findings.

SRCC has been associated with a poor prognosis compared with AC[5,6,10,11]. Studies have shown that peritoneal metastases of SRCC are associated with a poorer prognosis, and survival is even worse if other organs are also affected[26]. But in our study, patients with peritoneal metastases had similar OS as compared to those with non-peritoneal metastases. This may be due to small sample size of the study. Often, these metastases cannot be treated with curative intent. As of now, curative surgery is an option mainly limited to liver and lung metastases, which are the most common metastatic sites in AC patients. Systemic chemotherapy for peritoneal metastases may not yield the same results compared with hematogenous metastases due to blood-peritoneal barrier. As a result, outcome is poor in advanced SRCC cases[27].

The incidence of synchronous and metachronous peritoneal metastases in colorectal carcinoma (AC) seems to be in the range of 4%-5% (much lower than with SRCC)[26,28]. Studies have revealed that peritoneal carcinomatosis among patients with metastatic colorectal cancer is associated with a 30% reduction in overall survival (10.7 mo *vs* 17.6 mo)[29]. The overall survival of these patients is found to be less than 6 mo despite the use of 5FU and leucovorin based chemotherapy[30,31]. But palliative surgery and systemic chemotherapy, together have been shown to improve survival upto 12 mo in patients with isolated peritoneal metastases[29,32].

Hyperthermic intra-operative intra-peritoneal chemotherapy (HIPEC) has shown promising results for peritoneal metastases of colorectal origin[29]. Verwaal *et al*[29] reported outcome of 1427 patients with peritoneal metastases of colorectal origin treated with cytoreductive surgery (CRS) and HIPEC. Peri-operative morbidity and mortality were 34% and 3% respectively. Median hospital stay was 16 d. Median PFS was 15 mo and OS was 33 mo. Three- and five-year survival rates were 46% and 31% respectively. So authors concluded that CRS and HIPEC seems to be safe and beneficial in peritoneal metastases of colorectal origin[33]. But literature assessing benefit of HIPEC for SRCC is scarce and controversial with studies denying[34,35] and implying[36] benefit of HIPEC in this subgroup. But these reports are retrospective and are fraught with small sample sizes.

Recently, Hao *et al*[37] have proposed a study assessing the benefit of monoclonal antibody blocking EpCAM in CRC. This may be relevant in the further management

of SRCC as EpCAM also has altered expression in this subtype.

Klaver *et al*[38] have proposed a randomized controlled trial (COLOPEC) for assessing benefit of prophylactic HIPEC in patients at high risk of peritoneal carcinomatosis. They have included patients (non-metastatic) with T4 disease or on table tumor site perforation for prophylactic HIPEC followed by routine adjuvant chemotherapy. It has been postulated in assumption that very few patients with peritoneal carcinomatosis become eligible for CRS and HIPEC; as a result they have poor prognosis. So if a prophylactic HIPEC reduces the occurrence of peritoneal metastases in future, it may result in benefit in OS. The investigators have not considered signet ring cell pathology as inclusion criteria for the study; probably because of low incidence (1%-2%) of it in the western literature. A similar study may be considered in Indian patients with signet ring cell carcinoma to assess benefit of prophylactic HIPEC at the time of primary surgery as it has a peculiar tendency for isolated peritoneal recurrences and the incidence of this particular histopathological subtype seems to be higher in them (11.4%) as suggested by present study.

It is unclear whether different histological subtypes should influence treatment decisions, since it is often not addressed in clinical trials. In the literature, studies concerning outcome after adjuvant or palliative chemotherapy for SRCC are rare. However, due to the aggressive behavior and high incidence of SRCC in young patients, it is imperative to develop understanding of potential adjuvant treatment options as it is likely to alter quality of life and have significant socio-economic impact. Colonic SRCC are more likely to have peritoneal dissemination and poorer survival than rectal SRCC. So more aggressive treatment options, like HIPEC may be useful in these patients at the time of primary surgery or after peritoneal limited recurrence in order to improve survival and quality of life. This can only be addressed in a randomized control trial setting. Due to high nodal disease burden and high incidence of failure after curative surgery (up to 40%), more extended and/or aggressive adjuvant chemotherapy options should also be explored in this subset of population which is younger and is likely to tolerate the aggressive treatment better.

Signet ring colorectal cancer has poor prognosis. It has a higher incidence in Indian subcontinent. It affects young patients and has predilection for peritoneal dissemination.

Isolated peritoneal metastases as well as isolated peritoneal recurrences are very frequent in these patients. SRCC responds well to radiation. So whenever indicated, neoadjuvant radiation should be included in the treatment protocol for rectal SRCC.

More aggressive and/or extended chemotherapy schedules as well as prophylactic HIPEC at the time of primary surgery, especially for colonic tumors, should be explored in a trial setting in order to improve dismal survival in these patients.

COMMENTS

Background

Signet ring colorectal cancer (SRCC) is a subtype of colorectal adenocarcinoma. It tends to affect younger age group. Most of the patients present in stage III or IV. The most common site affected is rectosigmoid region. It has a peculiar affection for peritoneal lining. Most of the metastases and recurrences happen exclusively in the peritoneal cavity. Visceral metastases are rare. Average prognosis of these patients is poor. There is no effective adjuvant or palliative treatment for this entity. Early studies in the field of cytoreductionandhyperthermic intra-operative intraperitoneal chemotherapy (HIPEC) have shown promising results and prolongation of survival in peritoneal carcinomatosis of colorectal cancer. The trials are underway to test the impact of prophylactic HIPEC during primary surgery for cT4N1/2 diseases. Since SRCC has a different natural course than the conventional adenocarcinoma of colon, it may be worthwhile to evaluate the possible role of extended chemotherapy or prophylactic HIPEC at the time of curative surgery for SRCC.

Research frontiers

Currently trials are underway (COLOPEC and Prophylochip) to assess efficacy of prophylactic HIPEC in high risk colorectal cancers to prevent occurrence of peritoneal metastases and prolongation of survival. Though aggressive, SRCC has shown its peculiar nature to remain confined to peritoneal cavity in majority patients. This makes it a potential target for peritoneum directed therapies (Cytoreduction and HIPEC). Also monoclonal antibodies blocking EpCAM are being evaluated in CRC. This may be relevant in the further management of SRCC as EpCAM also has altered expression in this subtype.

Innovations and breakthroughs

Cytoreduction and HIPEC has shown survival benefit in peritoneal carcinomatosis of colorectal origin in a large randomized trial by Verwaal *et al* SRCC has not been evaluated widely in the western literature, probably due to lower incidence. But in Indian subcontinent, the incidence of this disease entity appears to be higher than rest of the world. It also affects younger population; as a result has significant bearing on the socioeconomic outcome of entire family. There is a strong need to develop a modified treatment protocol for this disease than conventional adenocarcinoma as the disease biology appears to be different and standard chemotherapy doesn't act well on the peritoneal disease. Certain molecular abnormalities are also noted in SRCC such as high microsatellite instability, EpCAM mutations, high-frequency of CpG island methylator phenotype, higher methylation level of long interspersed nucleotide element-1 and frequent *BRAF* mutation and low COX-2 expression. Further research needs to be carried out to understand the biology of this disease entity well which might give us an insight into potential treatment options for the same.

Applications

To summarize, SRCC seems to be a suitable target for peritoneum directed therapies which include aggressive cytoreduction and HIPEC. Extended/modified chemotherapy protocols may improve survival. Further understanding of molecular biology of this disease may open new methods for its treatment.

Peer-review

It is a retrospective study of an uncommon subtype of colorectal carcinoma. The author statisized some information of this cancer including the age, location, stages, metastasis, recurrence and survival.

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SYSTEMATIC REVIEWS

Colon adenoma features and their impact on risk of future advanced adenomas and colorectal cancer

Audrey H Calderwood, Karen E Lasser, Hemant K Roy

Audrey H Calderwood, Section of Gastroenterology, Department of Medicine, Dartmouth-Hitchcock Medical Center, Lebanon, NH 03756, United States

Karen E Lasser, Section of General Internal Medicine, Department of Medicine, Boston University School of Medicine, Boston, MA 02118, United States

Hemant K Roy, Section of Gastroenterology, Department of Medicine, Boston University School of Medicine, Boston, MA 02118, United States

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Correspondence to: Audrey H Calderwood, MD, MS, Section of Gastroenterology, Department of Medicine, Dartmouth-Hitchcock Medical Center, One Medical Center Drive, Lebanon, NH 03756, United States. audrey.h.calderwood@hitchcock.org
Telephone: +1-603-6505261
Fax: +1-603-6505225

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Abstract

AIM

To review the evidence on the association between specific colon adenoma features and the risk of future colonic neoplasia [adenomas and colorectal cancer (CRC)].

METHODS

We performed a literature search using the National Library of Medicine through PubMed from 1/1/2003 to 5/30/2015. Specific Medical Subject Headings terms (colon, colon polyps, adenomatous polyps, epidemiology, natural history, growth, cancer screening, colonoscopy, CRC) were used in conjunction with subject headings/key words (surveillance, adenoma surveillance, polypectomy surveillance, and serrated adenoma). We defined non-advanced adenomas as 1-2 adenomas each < 10 mm in size and advanced adenomas as any adenoma ⩾ 10 mm size or with > 25% villous histology or high-grade dysplasia. A combined endpoint of advanced neoplasia included advanced adenomas and invasive CRC.

RESULTS

Our search strategy identified 592 candidate articles

of which 8 met inclusion criteria and were relevant for assessment of histology (low grade *vs* high grade dysplasia, villous features) and adenoma size. Six of these studies met the accepted quality indicator threshold for overall adenoma detection rate > 25% among study patients. We found 254 articles of which 7 met inclusion criteria for the evaluation of multiple adenomas. Lastly, our search revealed 222 candidate articles of which 6 met inclusion criteria for evaluation of serrated polyps. Our review found that villous features, high grade dysplasia, larger adenoma size, and having ⩾ 3 adenomas at baseline are associated with an increased risk of future colonic neoplasia in some but not all studies. Serrated polyps in the proximal colon are associated with an increased risk of future colonic neoplasia, comparable to having a baseline advanced adenoma.

CONCLUSION

Data on adenoma features and risk of future adenomas and CRC are compelling yet modest in absolute effect size. Future research should refine this risk stratification.

Key words: Colon adenoma; Colorectal cancer screening; Surveillance; Colonoscopy

Core tip: The data on adenoma size, adenoma multiplicity and serrated polyps in terms of risk for future adenomas and colorectal cancer are compelling, however, the absolute effect size is relatively modest. Current guideline recommendations to perform colonoscopy surveillance at 3-5 years after baseline adenomas and serrated polyps appear appropriately tailored to the risk of future neoplasia.

Calderwood AH, Lasser KE, Roy HK. Colon adenoma features and their impact on risk of future advanced adenomas and colorectal cancer. *World J Gastrointest Oncol* 2016; 8(12): 826-834 Available from: URL: http://www.wjgnet.com/1948-5204/full/v8/i12/826.htm DOI: http://dx.doi.org/10.4251/wjgo.v8.i12.826

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and the second leading cause of cancer death among men and women in the United States[1]. The lifetime probability of developing CRC is approximately 5%, with 90 percent of cases occurring after age 50. In 2016, an estimated 134500 people will be diagnosed with CRC and 49200 will die of the disease[1].

The vast majority of CRCs arise from a histologically-specific type of colon polyp, the adenoma, which forms as a result of sporadic mutation in the adenomatous polyposis coli pathway or DNA mismatch repair and by definition contains low-grade dysplasia. Over many years, a minority of adenomas may grow in size and progress from low-grade dysplasia to high-grade dysplasia, to carcinoma-*in-situ* to invasive carcinoma. More recently, serrated adenomas (named for the "sawtooth" pattern in the crypts) have been identified as accounting for approximately 20%-30% of CRCs. In this review, we will use the term "adenoma" to describe adenomatous and serrated colon polyps and "serrated polyps" to specify polyps with serrated histology.

Colonoscopy is the most widely used modality for CRC screening[2,3]. Advantages of colonoscopy include the ability of endoscopists both to identify and remove adenomas, which decreases the risk of subsequent CRC[4]. By definition, "screening colonoscopy" occurs in patients without a history of adenomas and "surveillance colonoscopy" occurs at set intervals (usually 3-5 years) in patients with a history of adenomas to survey for new adenomas[5]. It is important to understand the existing evidence upon which surveillance colonoscopy recommendations are made to help inform shared decision making with patients who have co-morbid conditions or limited life expectancy[6]. This review will focus on the association between specific adenoma features and future colonic neoplasia.

MATERIALS AND METHODS

We searched the National Library of Medicine through PubMed for articles from 1/1/2003 to 5/30/2015. We did not search prior to 2003 because of technological advances in colonoscopy optics in 2002, which dramatically improved the diagnostic accuracy of colonoscopy; data prior to 2003 were not considered relevant to the current risk estimates of CRC after colonoscopy. We used the following filters: English language, human, age > 18, clinical trial, multicenter, prospective observational, meta-analysis. Specific MESH terms were used: Colon, colon polyps, adenomatous polyps, epidemiology, natural history, growth, cancer screening, colonoscopy, colorectal cancer. The MESH terms were used in conjunction with subject headings/key words: Surveillance, adenoma surveillance, polypectomy surveillance, and serrated adenoma. We excluded reviews, guidelines, editorials, case-control, cross-sectional and case series or reports.

We excluded studies of patients with inflammatory bowel disease, personal history of CRC, or family history of genetic CRC syndromes. We reviewed all abstracts for relevance. Full articles of the relevant abstracts were then reviewed with the quality of evidence graded by all three authors using the American Heart Association Evidence-Based Scoring System for Level of Evidence as follows: A: Data derived from multiple randomized clinical trials (RCTs); B: Data derived from a single randomized trial or nonrandomized studies; C: Consensus opinion of experts. The bibliographies of all included articles were also evaluated for additional articles by a single author [histology and size (AHC), multiple adenomas and serrated polyps (HKR)] then

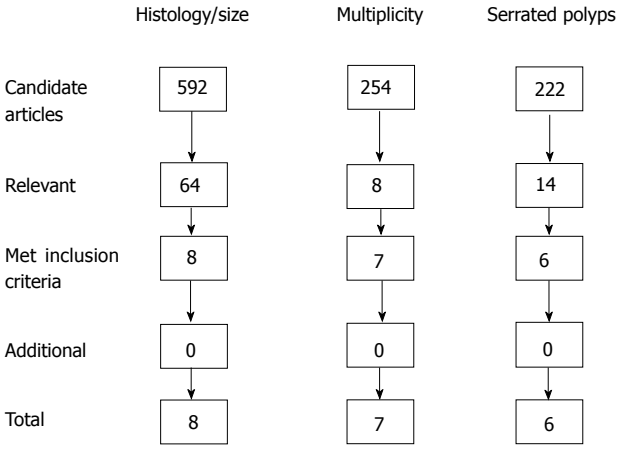

Figure 1 Results of the literature search. Literature search results evaluating the impact of histology and size of adenomas, number of adenomas, and serrated polyps on the risk of future advanced adenomas and colorectal cancer.

reviewed by all three authors for consensus.

We defined non-advanced adenomas as 1-2 adenomas each less than 10 mm in size[5]. We defined advanced adenomas as any adenoma ⩾ 10 mm size or with > 25% villous histology or high-grade dysplasia[5]. A combined endpoint of advanced neoplasia included advanced adenomas and invasive CRC.

RESULTS

Histology (low grade vs high grade dysplasia, villous features)

Our search strategy identified 592 candidate articles (Figure 1), of which 64 were relevant. We excluded 56 based on study design or absence of relevant primary outcome or predictors, leaving 8 studies (Table 1). Six of these studies met the accepted quality indicator threshold for overall adenoma detection rate (ADR) > 25% among study patients[7], including one study that explicitly described that ADR was > 25% for each individual endoscopist in study[8]. ADR was only 22% in the study by Bonithon-Kopp *et al*[9] and the meta analysis by Saini *et al*[10] did not present information on ADR.

A small to moderate association between adenoma histology and risk of future advanced adenomas and CRC with variable significance was found among the 8 studies. Four studies[11-14], including a pooling project of 8 prospective RCTs (evidence level A), found that villous histology was a significant risk factor for future advanced neoplasia (adjusted OR = 1.3; 95%CI: 1.1-1.5)[14]. Of note, the relative risk (RR) in Lieberman's study (6.1; 95%CI: 2.5-14.7) is higher compared to the other studies because the comparator was subjects without any neoplasia, in contrast to subjects with adenomas without villous histology used in the other studies. In addition, Lieberman studied a Veteran's Affairs (VA) population who are known to have higher rate of baseline adenomas compared to non-VA patients[12]. A prospective cohort study of 1086 patients with a median of 10.5 years of follow-up found that villous histology within an adenoma increased the relative risk of any future adenoma (1.8; 95%CI: 1.2-2.6) (evidence level B)[15]. A primary RCT[9], a meta analysis of 5 studies[10], and a prospective cohort study[8] found no association of villous histology with future neoplasia (evidence level B).

Similarly, histological findings of high-grade dysplasia had a small and variable association with risk of advanced neoplasia. The meta-analysis by Saini *et al*[10] found an increased RR of 1.8 (95%CI: 1.1-3.2)[10], whereas the primary RCT[9], pooling project[14], and prospective registry study[13] found no association (evidence level A). A prospective cohort study found that compared to an external control population, patients with high-grade dysplasia at baseline had an elevated SIR for CRC of 2.8 (95%CI: 0.3-10.2) compared to the reference group without high grade dysplasia (SIR 0.52; 95%CI: 0.3-0.95)[15]. In Lieberman's prospective study of 1193 VA patients, he found a RR of advanced neoplasia of 6.8 (95%CI: 2.6-18.1) compared to those with no neoplasia at baseline[12].

In summary, villous histology within an adenoma may have a small association with future advanced neoplasia, however this was not seen uniformly across all studies. Compared to having no adenomas at baseline, adenomas with high-grade dysplasia are associated with an increased risk of future advanced neoplasia; however, compared to having adenomas that do not contain high-grade dysplasia, the association with future advanced neoplasia is small and variable depending on the study.

Size

We used the same search strategy for histology to evaluate the impact of adenoma size on risk of future colonic neoplasia, finding the same 8 studies (Table 2)[8-15]. Larger adenoma size at baseline increased the risk of future advanced neoplasia. In Martinez's pooling project of 8 prospective RCTs, the risk of advanced neoplasia increased for each increase in size category (evidence level A). When adenomas < 5 mm were considered the reference group, those with adenomas 10-19 mm and adenomas ⩾ 20 mm had a RR of 2.3 (95%CI: 1.8-2.8) and 3.0 (95%CI: 2.2-4.0), respectively[14]. Similarly, four other prospective studies found that adenomas ⩾ 10 mm imparted an increased RR of future advanced neoplasia ranging from 1.7 (95%CI: 1.2-2.3) to 3.0 (95%CI: 1.8-5.1) and 6.4 (95%CI: 2.7-14.9) (level of evidence B)[8,12,13]. On the other hand, Saini's meta-analysis of 5 studies and a primary RCT, the European Fiber-Calcium Intervention trial (in which 552 patients with resected adenomas randomized to calcium and soluble fiber underwent surveillance colonoscopy at 3 years) failed to show any association between adenoma size and future advanced neoplasia (evidence level B)[9,10]. A prospective study by Bertario of 1086 patients did not show an association between polyp size ⩾ 10 mm and SIR of advanced

Table 1 Articles summarizing the risk of neoplasia based on the histology of polyps seen at baseline colonoscopy

Ref.	Sample size	Median follow-up, yr	Predictor	Primary outcome	Absolute risk of outcome (%)	RR[1] [95%CI]
RCT						
Laiyemo *et al*[11]	1905	4	Villous	ACN	9 (7-11) *vs* 5 (4-6)	2.3 [1.5-3.4]
Bonithon-Kopp *et al*[9]	552	3	HGD	ACN	9.8 *vs* 5.5	1.9 [1.0-3.6]
			Villous		10.3 *vs*. 6.8	1.7 [0.8-3.7]
Pooled analysis						
Martínez *et al*[14]	8 studies	3.9	HGD	ACN	16.0 (13.2-18.7) *vs* 10.6 (9.8-11.3)	1.1 [0.8-1.4]
	9167		Villous		16.8 (15.1-18.5) *vs* 9.7 (9.0-10.4)	1.3 [1.1-1.5]
Meta-analysis						
Saini *et al*[10]	5 studies	3	HGD	ACN	4% risk difference (0-8)	1.8 [1.1-3.2]
			Villous		2% risk difference (-1 to 4)	1.3 [1.0-1.7]
Prospective						
Bertario *et al*[15]	1086	10.5	HGD	CRC	2.8 SIR (0.3-10.2) *vs* 0.52	Not available
			Tubulovillous	Any adenoma	Not available	1.3 [1.0-1.6]
			Villous			1.8 [1.2-2.6]
[2]Lieberman *et al*[12]	1193	5.5	No adenomas	ACN	2.4	Ref
			HGD		17	6.8 [2.6-18.1]
			Villous		16	6.1 [2.5-14.7]
Chung *et al*[8]	3808	4.5	Villous	ACN	Not available	1.5 [0.7- 3.0]
Registry						
Van Heijningen *et al*[13]	2990	2	HGD	AA	13	1.2 [0.8-1.8]
			Villous		8	2.0 [1.2-3.2]
			HGD	ACN	11	Not available
			Villous		17	

[1]Relative risk compared to patients adenomas without the predictor characteristics. Adenomas with villous compared to those without adenomas with villous features (as opposed to those without any adenomas). [2]Relative risk compared to those with no neoplasia. ACN: Advanced colonic neoplasia (includes advanced adenomas and colorectal cancer); AA: Advanced adenomas; CRC: Colorectal cancer; HGD: High grade dysplasia; RCT: Randomized control trial.

Table 2 Articles summarizing the risk of future colonic neoplasia based on the size of polyps seen at baseline colonoscopy

Ref.	Sample size	Median follow-up, yr	Predictor	Primary outcome	Absolute risk of outcome (%)	RR [95%CI]
RCT						
Laiyemo *et al*[11]	1905	4	⩾ 10 mm	ACN	9 (7-11) *vs* 5 (4-6)	0.9 [0.6-1.4]
Bonithon-Kopp *et al*[9]	552	3	⩾ 10 mm	ACN	7.1 *vs* 7.8	1.1 [0.5-2.1]
Pooled analysis						
Martínez *et al*[14]	8 studies	3.9	< 5 mm	ACN	8.7 (7.7-9.7)	Ref
	9167		10-19 mm		15.9 (14.5-17.4)	2.3 [1.8-2.8]
			⩾ 20 mm		19.3 (16.4-22.3)	3.0 [2.2-4.0]
Meta-analysis						
Saini I *et al*[10]	5 studies	3	⩾ 10 mm	ACN	2% risk difference (-2 to 6)	1.4 [0.9-2.3]
Prospective						
Bertario *et al*[15]	1086	10.5	⩾ 20 mm	Any adenoma	Not available	1.5 [1.1-2.1]
				CRC	SIR	Not available
			Baseline		0.52 [0.3-0.9]	
			< 10 mm		0.33 [0.1-0.9]	
			⩾ 10 mm		0.82 [0.3-1.8]	
Lieberman *et al*[12]	1193	5.5	⩾ 10 mm	ACN	15.5 *vs* 2.4	6.4 [2.7-14.9]
Chung *et al*[8]	3808	4.5	⩾ 10 mm	ACN	Not available	3.0 [1.8-5.1]
Registry						
Van Heijningen *et al*[13]	2990	2	⩾ 10 mm	AA	8 *vs* 4	1.7 [1.2-2.3]

ACN: Advanced colonic neoplasia (includes advanced adenomas and colorectal cancer); AA: Advanced adenomas; CRC: Colorectal cancer; RCT: Randomized control trial; SIR: Standard incidence ratio.

neoplasia (evidence level B)[15].

In summary, adenoma size ⩾ 10 mm appears to be associated with future advanced neoplasia and the magnitude of risk increases for larger adenomas ⩾ 20 mm in size.

Multiple adenomas

Our search strategy revealed 254 articles of which 7 met inclusion criteria (Figure 1). Van Heijningen *et al*[13] noted that among 2990 consecutive colonoscopies in the Netherlands, there was an increased risk of

Table 3 Articles summarizing the risk of colonic neoplasia based on the number of polyps seen at baseline colonoscopy

Ref.	Sample size	Median follow-up, yr	Predictor	Primary outcome	Absolute risk of outcome (%)	RR [95%CI]
RCT						
Laiyemo *et al*[11]	1905	4	⩾ 3 adenomas	ACN	10 (7-14) *vs* 6 (5-7)	1.5 [1.0-2.2]
Bonithon-Kopp *et al*[9]	552	3	⩾ 3 adenomas	ACN	18.1 *vs* 5.0	2.7 [1.2-6.4]
Meta-analysis						
Saini I *et al*[10]	5 studies	3	⩾ 3 adenomas	ACN	5% risk difference (1-10)	2.5 [1.1-6.0]
Prospective						
[1]Lieberman *et al*[12]	1193	5.5	1-2	ACN	4.6	1.9 [0.8-4.4]
			⩾ 3		11.9	5.0 [2.1-12.0]
Chung *et al*[8]	3808	4.5	⩾ 3 adenomas	ACN	Not available	3.1 [1.5-6.6]
Registry						
Van Heijningen *et al*[13]	2990	2	1	AA	4	Ref
			2		7	1.6 [1.1-2.4]
			3		8	2.1 [1.3-3.4]
			4		12	2.0 [0.9-4.6]
			⩾ 5		18	3.3 [1.7-6.6]
Ng *et al*[18]	4989	2		AA	Not available	Adjusted OR
			1			3.6 [2.6-5.0]
			2			7.1 [4.9-10.4]
			3			13.7 [0.9-4]

[1]Relative risk compared to those with no neoplasia. ACN: Advanced colonic neoplasia (includes advanced adenomas and colorectal cancer); AA: Advanced adenomas; OR: Odds ratio; RCT: Randomized control trial.

advanced adenomas on surveillance exams depending on number of adenomas at initial screening colonoscopy (Table 3)[13]. Using participants with one adenoma as the reference group, those with 2, 3, 4 and ⩾ 5 adenomas at baseline colonoscopy had 1.6 (95%CI: 1.1-2.4), 2.1 (95%CI: 1.3-3.4), 2.0 (95%CI: 0.9-4.6) and 3.3 (95%CI: 1.7-6.6) times the relative risk of future advanced adenomas, respectively (evidence level B)[13]. Lieberman *et al*[12] evaluated 1193 Veterans undergoing surveillance colonoscopy 5 years after baseline colonoscopy. Compared to those who were neoplasia-free at baseline, patients with 1-2 small adenomas and ⩾ 3 adenomas had a RR of advanced adenoma at follow-up of 1.9 (95%CI: 0.83-4.4) and 5.0 (95%CI: 2.1-12.0), respectively, the latter of which was comparable to the risk of having a single advanced adenoma at baseline (evidence level A).

Bonithon-Kopp *et al*[9] found that in the European Fiber-Calcium Intervention trial, patients with ⩾ 3 adenomas had a HR of 5.5 (95%CI: 2.4-12.6) of developing advanced adenomas at three year colonoscopy but only if one of the adenomas was proximal - if all the adenomas were distal, there was no increase in risk of advanced adenomas (0.83; 95%CI: 0.18-3.9) (evidence level A)[9]. Analysis of 4 year surveillance colonoscopy data from the Polyp Prevention Trial (n = 1905) found that compared to having one non-advanced adenoma, individuals with 2 or ⩾ 3 adenomas had a RR for advanced neoplasia of 1.38 (95%CI: 0.92-2.1) and 1.84 (95%CI: 1.2-2.8), respectively[11]. Finally, a meta-analysis of older literature found that those with ⩾ 3 adenomas at index colonoscopy were more likely to have recurrent advanced adenomas than were patients with 1 to 2 adenomas (RR = 2.5; 95%CI: 1.1-6.0) (evidence level B)[10]. In summary, these data suggest that adenoma number may confer a risk of future neoplasia comparable to adenoma size and as discussed below may be further influenced by the quality of the performance of colonoscopy.

Serrated polyps

Our search revealed 222 candidate articles of which 6 met inclusion criteria (Figure 1). Four were mainly cross-sectional studies, which evaluated the presence of concurrent adenomas and two evaluated the correlation with future neoplasia (Table 4). In a study of 10199 subjects, having a large serrated polyp ⩾ 1 cm (LSP) was associated with an increased odds of concurrent advanced neoplasia (adjusted OR = 4.0; 95%CI: 2.8-5.7) and CRC (adjusted OR = 3.3; 95%CI: 2.2-5.0) compared to those who were neoplasia-free (evidence level B)[16]. Álvarez *et al*[17] reported that in 5059 patients randomized to undergo screening colonoscopy *vs* stool test, LSPs were associated with concurrent proximal (OR = 4.2; 95%CI: 1.7-10.2) and distal (OR = 2.6; 95%CI: 1.5-4.6) advanced neoplasia. Several other studies corroborate the relationship between proximal LSPs and concurrent advanced adenomas[18,19].

With regard to future lesions, a secondary analysis of a large randomized flexible sigmoidoscopy study from Norway that included a median follow-up of 10.9 years provides some insights (evidence level A)[20]. Having a LSP was associated with an increased risk of future CRC (adjusted OR = 3.3; 95%CI: 1.3-8.6), comparable to having a baseline advanced adenoma. Interestingly, none of the other serrated polyps left *in situ* developed CRC in that tumor, suggesting the serrated polyps might be a marker of field carcinogenesis rather than a precursor lesion[20]. Schreiner *et al*[21] found that

Table 4 Risk of concurrent and future advanced adenomas and colon cancer based on serrated polyps

Ref.	Sample size	Median follow-up, yr	Predictor	Primary outcome	Absolute risk	Risk [95%CI]
RCT						
Holme *et al*[20]	100210	10.9	⩾ 10 mm serrated polyp	Future CRC	3.4 *vs* 1.4 cases/1000 patient years	HR 3.3 [1.3-8.6]
Registry						
Álvarez *et al*[17]	5059	None	Proximal l ⩾ 10 mm	ACN	Not available	4.2 [1.7-10.2]
			Distal l ⩾ 10 mm			2.6 [1.5-4.6]
			Proximal HP			1.6 [1.3-2.3]
Hiraoka *et al*[16]	10199	None	⩾ 10 mm serrated polyps	ACN		4.0 [2.8-5.7]
				CRC	Not available	3.3 [2.2-5.0]
				Proximal CRC		4.8 [2.5-8.4]
Hazewinkel *et al*[19]	1426	None	Proximal SP	ACN	Not available	2.4 [1.6-3.8]
			Proximal HP			2.0 [1.1-3.4]
			Prox SSA/P			3.0 [1.5-6.2]
			⩾ 10 SP			4.0 [1.9-8.6]
			⩾ 10 mm HP			3.2 [1.1-9.1]
			⩾ 10 mm SSA/P			5.0 [1.7-14.9]
Ng *et al*[18]	4989	None	SSA	ACN	Not available	4.5 [2.4-8.5]
			Proximal SP			2.2 [1.4-3.6]
			⩾ 10 mmSP			59.3 [18.9-186.2]
			⩾ 3 SP			4.9 [1.2-19.2]
			⩾ 3 non-advanced adenomas			3.6 [2.6-5.0]
Schreiner *et al*[21]	3121	None	Proximal SP	AA	17.3 *vs* 10.0	1.9 [1.3-2.7]
			⩾ 1 cm SP		27.3 *vs* 10.3	3.4 [1.7-6.7]
	1371	5.5	Proximal SP without adenomas	Future AA	5.1 *vs* 2.7	3.1 [1.6-6.2]
			Proximal SP with nonadvanced adenoma		7.9 *vs* 6.3	1.2 [0.5-3.8]
			Proximal SP with advanced adenoma		28.9 *vs* 14.7	2.3 [1.0-5.0]

AA: Advanced adenomas; ACN: Advanced colonic neoplasia (includes advanced adenomas and cancer); HP: Hyperplastic polyp; HR: Hazard ratio; RCT: Randomized control trial; SP: Serrated polyp; SSA: Sessile serrated adenoma.

patients with proximal non-dysplastic serrated polyps followed for median of 5.5 years had an increased odds for future adenomas of 3.1 (95%CI: 1.6-6.2) compared to those who were polyp free at baseline (evidence level B). Thus, while it is clear that certain serrated polyps can progress to CRC, those that are right sided and/or ⩾ 1 cm are associated with future neoplasia and are a marker for concurrent adenomas and need to be considered as equivalent to an adenoma from a surveillance perspective.

DISCUSSION

Our review found that specific histologic features of adenomas (*i.e.*, high grade dysplasia and villous features) are associated with a small risk of future advanced adenomas though data was inconsistent across studies (level B evidence). In particular, villous features did not confer a consistent or significant association, suggesting it may not be an important risk factor for future advanced adenomas. Data was even more inconsistent for adenoma size, although the linear association between size and risk is compelling (level B evidence). Size itself is challenging to determine reliably because of the lack of a standardized method for estimating adenoma size and the inter-observer variability among size estimation endoscopically as well as differences in estimations between endoscopic and pathology measurements[22,23]. Use of an open biopsy forceps as a reference standard for measurement during colonoscopy was accurate to the millimeter only 37% of the time[24]. The variability in estimating size of adenomas is concerning given that a 1 mm difference in size can change surveillance by 2 years. In a prospective study using size on pathology as gold standard, endoscopists mis-sized polyps 63% of the time, leading to inappropriate surveillance intervals 35% of the time[25]. Relying on pathology reports for size estimates is challenging, given that polyps are often removed piecemeal and can be fragmented during retrieval. Thus, the accuracy of size estimates for determining surveillance intervals should be viewed cautiously.

Having ⩾ 3 adenomas at baseline is associated with an increased risk of future colonic neoplasia (level B evidence), particularly if at least one adenoma is located in the proximal colon, although more supporting data is needed. The findings of our study echo those of the seminal prospective randomized National Polyp Study[26], in which multiple adenomas (⩾ 3; OR = 6.9; 95%CI: 2.6-18.3) and large adenomas (OR = 2.2; 95%CI: 0.6-7.8) were associated with future advanced adenomas at surveillance. In that study, however only multiplicity was a significant risk factor ($P < 0.001$). The risk conferred by villous features or high grade dysplasia

Table 5 Current guideline recommendations for surveillance based on from United States Multi-society Task Force on colorectal cancer, British Society of Gastroenterology, and European Society of Gastrointestinal Endoscopy[5,27,28]

Organization and year of guidelines	Recommendations for surveillance of adenomas	
	Baseline finding	Timing of next exam, yr
USMSTF on CRC[5], 2012	1-2 small adenomas	5-10
	Adenoma with villous histology	3
	Adenoma with high grade dysplasia	3
	Adenoma ⩾ 10 mm	3
	3-10 adenomas	3
	Serrated polyps:	
	< 10 mm no dysplasia	5
	⩾ 10 mm	3
	Dysplasia	3
	Traditional serrated adenoma	3
British Society of Gastroenterology[28], 2010	1-2 small adenomas	5-10
	3-4 small adenomas	3
	Adenoma ⩾ 10 mm	3
	⩾ 5 small adenomas	1
	⩾ 3 at least one ⩾ 10 mm	1
European Society of Gastrointestinal Endoscopy[27], 2010	High risk adenomas:	3
	Adenoma ⩾ 10 mm	
	Adenomas with high grade dysplasia	
	Villous component	
	⩾ 3 adenomas	
	Serrated polyp ⩾ 10 mm	
	Serrated polyps with dysplasia	
	Not high risk adenomas	10

CRC: Colorectal cancer; USMSTF: United States Multi-society Task Force.

at baseline was not included.

Current United States and European guidelines recommend repeat colonoscopy in 3 years for patients with ⩾ 3 adenomas or any adenoma ⩾ 10 mm size or with high grade dysplasia or villous features compared to 5-10 years for those with 1-2 small adenomas (Table 5)[5,27]. The British guidelines do not take into account advanced histology and recommend earlier follow-up at 1 year for those with at least 5 small adenomas or 3 adenomas if one is ⩾ 10 mm in size[28]. Current level B evidence demonstrates a higher risk of future colonic neoplasia based on having a large serrated polyp (OR ranging from 3.3-4.2) and supports earlier surveillance at 3 years as recommended by guidelines in this group[5,28]. The recommendations for surveillance of serrated polyps are identical to adenomas[5]. While surveillance guidelines may be based primarily on adenoma features and risk of future neoplasia, they may also be influenced by national economics and local culture around population-based screening and surveillance, which can vary by country and continent.

The way in which very small differences in adenoma size and number (*e.g.*, 2 *vs* 3 adenomas) can affect timing of recommended surveillance (from 3 to 5 years) emphasizes the importance of the quality of the colonoscopy performed. Adenoma detection rate (ADR) is considered the most important quality metric in the performance of colonoscopy because it is a close surrogate measure for interval CRC rates and can be measured feasibly[7,29]. Other important quality metrics include cecal intubation rates and bowel preparation quality, both of which impact ADR[7]. A recent simulation study demonstrated that ADR correlates with a lower lifetime risk of CRC without an increase in cost, thus further underscoring the importance of colonoscopy quality[30]. As ADR improves overall whether from improved endoscope optics or adjunctive techniques (*e.g.*, narrow band imaging, caps, rings)[31], the association between baseline colonic neoplasia findings and risk of future neoplasia may need to be reassessed.

Our review has certain limitations. We do not address the impact of other factors besides adenoma features on risk for CRC, which are beyond the scope of this article. However, since CRC involves the interactions of genes and the environment, other factors such as family history, age, smoking, diabetes, and obesity have the potential to impact the risk of recurrent neoplasia. Indeed, the NIH risk score looks at a variety of these factors, although its predictive ability has been modest[32]. We also did not consider the location (proximal *vs* distal) of adenomas in this review. Location may impart a differential neoplastic risk, with proximal lesions portending a higher risk for recurrence, and merits further clarification in terms of biological underpinnings and clinical strategies. The duration of follow-up for most of the studies ranged from 2 to 5.5 years, which does not allow for the assessment of long-term outcomes. However, this time frame is in line with current surveillance guideline recommendations and provides an adequate follow-up period for the evaluation of the risk of recurrent neoplasia. Lastly, the existing data do not explicitly compare the risk of future advanced adenomas at surveillance based on having multiple different risk factors simultaneously, likely due to limitations of sample size and loss of power with subgroup comparisons. However, if multiple independent risk factors were identified (*e.g.*, multiplicity and size), then having those simultaneously would increase the individual's overall risk of future advanced adenomas.

Future research should continue to evaluate the risk of CRC based on multiple factors incorporating serial colonoscopy information. A few studies have attempted to predict the risk of future neoplasia based on 2 or more examinations[11,33]. In addition, other biomarkers of the risk of CRC are needed. Since colorectal carcinogenesis involves both genetic and exogenous risk factors of which approximately half are modifiable (*i.e.*, obesity and smoking)[34], assessment of risk at the level of the colonic mucosa where the interaction between genetics and environment plays out locally may provide a novel approach. While there are a plethora of candidate biomarkers of field carcinogenesis (*e.g.,* molecular alterations such as methylation, gene expression, microRNA in the normal rectal epithelium), the adenoma is currently the only predictor of risk that is robust enough and practical for use in clinical

practice. Future research should also explore the impact of life expectancy on surveillance colonoscopy to guide clinicians who must weigh the risks and benefits for individual patients.

In conclusion, current United States Multi-Society Task Force on CRC recommendations to perform colonoscopy surveillance at 3-5 years after baseline adenomas and serrated polyps appear appropriately tailored to the risk of future neoplasia. The data on adenoma size, adenoma multiplicity and serrated polyps in terms of risk for future adenomas and CRC are compelling, however, the absolute effect size is relatively modest. Future research should identify methods of stratifying a patient's risk for CRC based on serial colonoscopy exams and could include composite risk scores and biomarkers.

COMMENTS

Background

Patients with adenomas of the colon undergo routine surveillance colonoscopy to survey for new adenomas. It is important to understand the existing evidence upon which surveillance colonoscopy recommendations are made.

Research frontiers

This review focuses on the association between specific adenoma features and the risk of future colonic neoplasia.

Innovations and breakthrough

This comprehensive review of the literature shows that adenoma size, adenoma multiplicity and serrated polyps increase the risk for future adenomas and colorectal cancer (CRC), however, the absolute effect size is relatively modest.

Applications

Current United States Multi-Society Task Force on CRC recommendations to perform colonoscopy surveillance at 3-5 years after baseline adenomas and serrated polyps appear appropriately tailored to the risk of future neoplasia.

Terminology

"Surveillance colonoscopy" refers to colonoscopy performed at set intervals (usually 3-5 years) in patients with a history of adenomas to survey for new adenomas.

Peer-review

This is a well-written comprehensive review of current literature on colon adenoma features and CRC risk. To add value to the manuscript, summarising guidelines round the world to provide the readers a more comprehensive review of suggested evidence and protocols would be proposed.

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CASE REPORT

Esophageal liposarcoma: Well-differentiated rhabdomyomatous type

Hisham M Valiuddin, Arianna Barbetta, Benedetto Mungo, Elizabeth A Montgomery, Daniela Molena

Hisham M Valiuddin, Lake Erie College of Osteopathic Medicine Bradenton, Bradenton, FL 34211, United States

Arianna Barbetta, Daniela Molena, Thoracic Surgery Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, New York, NY 10065, United States

Benedetto Mungo, Division of Thoracic Surgery, Department of Surgery, John Hopkins Hospital, Baltimore, MD 21218, United States

Elizabeth A Montgomery, Division of Gastrointestinal and Liver Pathology, Department of Pathology, John Hopkins Hospital, Baltimore, MD 21218, United States

Author contributions: Molena D designed the study, surgically retrieved tumor, and followed up findings; Montgomery EA analyzed specimen, detailed pathology, documented findings and reviewed figures; Barbetta A and Mungo B researched literature and reviewed manuscript; Valiuddin HM conducted literature review, collected data and drafted manuscript.

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Correspondence to: Daniela Molena, MD, Director of Esophageal Surgery, Thoracic Surgery Service, Department of Surgery, Memorial Sloan Kettering Cancer Center, 1275 York Avenue, New York, NY 10065, United States. molenad@mskcc.org
Telephone: +1-212-6393870
Fax: +1-212-6462277106

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Abstract

Rhabdomyomatous well-differentiated esophageal liposarcomas are extremely rare. As of August 2016, only one other such case has been reported in the English-language medical literature. Liposarcomas in general are one of the most common soft tissue neoplasms in adults, but the incidence of primary esophageal liposarcomas is exceptionally low. There have been only 42 reported cases of primary liposarcoma of the esophagus worldwide thus far. These malignancies are harbored within giant fibrovascular polyps, which slowly grow within the esophageal lumen causing obstructing symptoms. We hereby present the case of a 68-year-old male patient who came in with a 2-mo history of worsening intermittent dysphagia, persistent cough, and postprandial retrosternal pain. After an esophagogastroduodenoscopy, a computed tomographic scan, and a diagnostic endoscopy, complete endoscopic resection was performed of the 13 cm × 6 cm × 2.6 cm fibrovascular polyp. A literature review was done and results are presented herein.

Key words: Esophageal cancer; Esophageal surgery; Endoscopy/endoscopic procedures; Pathology esophagus; Liposarcoma; Mesenchymal tumor

Core tip: This is only the second case of a rhabdomyomatous well-differentiated esophageal liposarcoma to be reported in the literature. Both cases clinically presented as standard esophageal liposarcomas housed in a giant fibrovascular polyp until histological examination by pathology. Given the rarity of the disease, there are only a few studies outlining its optimal management, nevertheless, diagnosis and treatment of this pathology can be approached by customary means, bearing extremely favorable prognosis.

Valiuddin HM, Barbetta A, Mungo B, Montgomery EA, Molena D. Esophageal liposarcoma: Well-differentiated rhabdomyomatous type. *World J Gastrointest Oncol* 2016; 8(12): 835-839 Available from: URL: http://www.wjgnet.com/1948-5204/full/v8/i12/835.htm DOI: http://dx.doi.org/10.4251/wjgo.v8.i12.835

INTRODUCTION

Primary esophageal liposarcomas are rare, with only 42 cases being reported in English-language literature as of August 2016[1]. Histologically, liposarcomas can be further classified into 4 subtypes based on their degree of differentiation: Dedifferentiated, well-differentiated, myxoid, or pleomorphic[2]. We present the case of a patient who had an esophageal well-differentiated liposarcoma containing rhabdomyomatous cells, of which, only one other case - to the best of our knowledge - has ever been reported[3].

CASE REPORT

A 68-year-old Caucasian male presented with a 2-mo history of worsening intermittent dysphagia, persistent cough, and postprandial retrosternal pain. He also complained of persistent dull pain on the left side of his neck, radiating to his left ear, which was not related to meals.

Suspecting gastroesophageal reflux disease, the patient was started on proton pump inhibitor pharmacotherapy. Upon no relief of symptoms, the patient was referred to an otolaryngologist to evaluate the pharynx with a laryngoscopy; no abnormalities were seen, and therefore the patient was referred to a gastroenterologist. An esophagram was first performed, which showed a voluminous intraluminal lesion within the thoracic esophagus, possibly being a neoplastic process such as a leiomyoma (Figure 1). An esophagogastroduodenoscopy was then performed, identifying a polypoid mass, which started at the level of the upper esophageal sphincter with a single stalk and extended all the way down to the esophagogastric junction. The polyp occupied about a third of the esophageal lumen, was heterogeneous in surface appearance, and consistent with a giant fibrovascular polyp; concurrently a small hiatal hernia was also seen. Biopsies from the head of the polyp

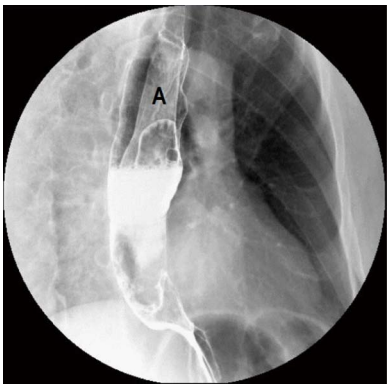

Figure 1 Barium esophagram showing an (A) obstructing intraluminal mass in the thoracic esophagus.

exhibited benign squamous mucosa with mild acute and chronic inflammation. A computed tomographic (CT) scan of the chest showed a large mass along the entire course of the esophagus (Figure 2). After an endoscopic ultrasound excluded the presence of major vessels within the main stalk, endoscopic resection was pursued. While using a flexible esophagoscope to visualize the mass, a snare was passed around the distal end of the polyp on retroflexion and then pulled up around the stalk, which was located on the left side of the esophagus just at the level of the upper esophageal sphincter. The proximal stalk was cauterized and divided with the snare, causing the polyp to drop into the distal esophagus. The polyp was then retrieved transorally using the endoscope and the snare to bring the mass to the level of the upper esophageal sphincter, followed by a laryngoscope and a clamp to extract it from the hypopharynx.

Pathology identified the 13.0 cm × 6.0 cm × 2.6 cm specimen as a well-differentiated liposarcoma arising in a giant fibrovascular polyp. Grossly the polyp had tan uniform surface without stigma of hemorrhage or necrosis (Figure 3). Histologically the polyp showed a central core of adipose and fibrovascular tissue surrounded by overlying squamous mucosa (Figure 4). An immunohistochemical stain for MDM-2 supported the diagnosis of liposarcoma (Figure 5). Focal areas of ossification were noted. In addition, there were scattered atypical cells with abundant eosinophilic cytoplasm, positive for desmin and also focally myogenin positive (Figure 6). The rhabdomyomatous differentiation is considered a low grade lesion (Figure 7).The final resection margin was uninvolved by the tumor. Patient recovered uneventfully and was discharged from the hospital on postoperative day 1. On follow up visit at 4 years, patient still has complete resolution of dysphagia, cough, neck and chest pain. He has been eating well and gained 15 pounds to date. Annual endoscopies and CT scans confirm no reoccurrence thus far.

DISCUSSION

Esophageal liposarcomas reside in giant fibrovascular

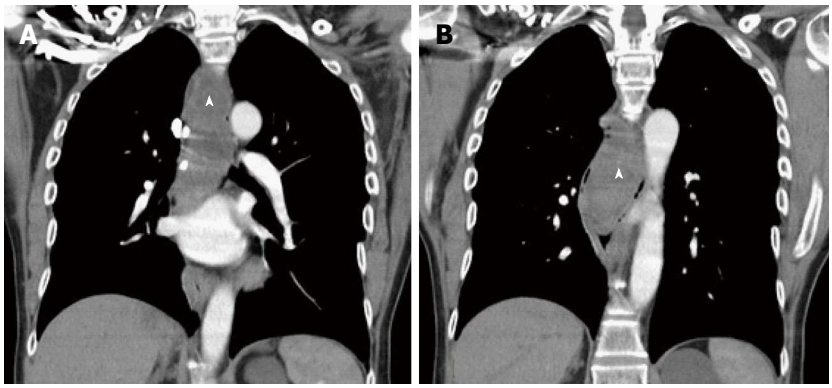

Figure 2 Computed tomographic scan of the chest (A) (B) showing a (arrowhead) large mass traversing the length of the esophagus.

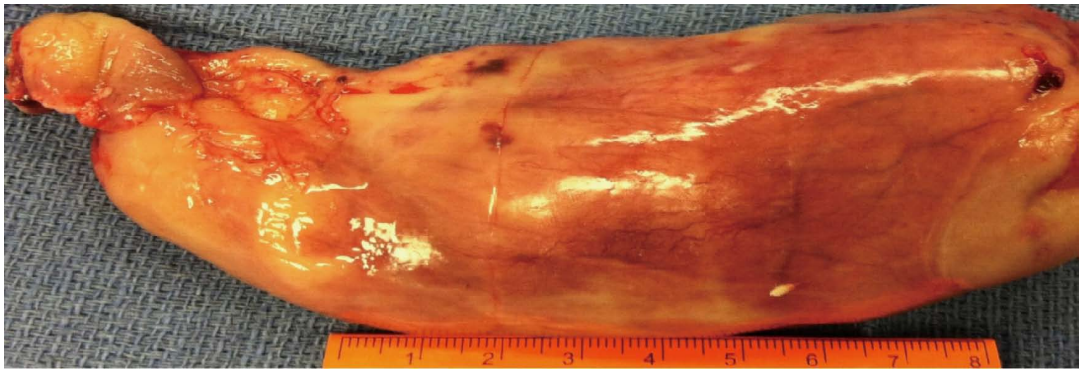

Figure 3 A macroscopic view of the resected giant fibrovascular polyp (13 cm × 6 cm × 2.6 cm) with uniform surface and a large single stalk.

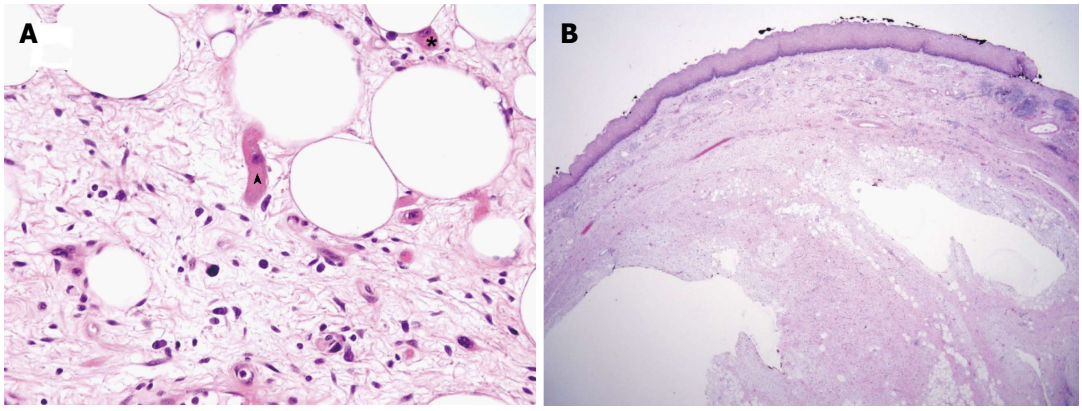

Figure 4 Histologically the polyp showed a central core of adipose and fibrovascular tissue surrounded by overlying squamous mucosa. A: Hematoxylin and eosin stain × 40 identifying (arrowhead) striated muscle cells and adipose tissue within the core of the esophageal liposarcoma; B: The giant polyp is characterized by a central core of adipose and fibrovascular tissue surrounded by overlying squamous mucosa.

polyps and are rare, consisting of 0.5% of all esophageal neoplasms[4]. Of the histologic sub classifications, well-differentiated type are the most common, with a prevalence of approximately 68%; myxoid being 20%; dedifferentiated and pleomorphic at 6% each[5]. The pathophysiology of esophageal giant fibrovascular polyps is unknown. The only theory with consensus is that an erroneous out-pouching of loose submucosal tissue undergoes traction and peristaltic forces causing it to insidiously grow and elongate into the lumen[3]. The average size of a giant fibrovascular polyp is approximately 13 cm in length, and 3.5 cm in width[3,5]. Liposarcomas are believed to originate from primitive mesenchymal cells rather than mature adipocytes[2]. The average age of onset of symptoms is 58.4 years, ranged from 38 to 73 years[4,5]. There has been a 72% male predominance of reported cases[5]. Almost all lesions were polypoid, except for a couple that were transmural[5,6]. Eighty percent of the liposarcomas described have been from the cervical portion of the

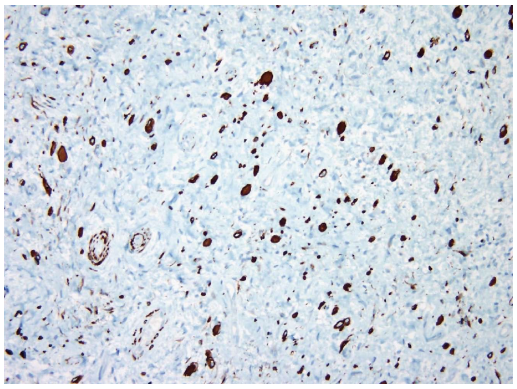

Figure 5 Immunohistology showed positive nuclear staining of lipoblasts with MDM2 confirming the diagnosis of liposarcoma.

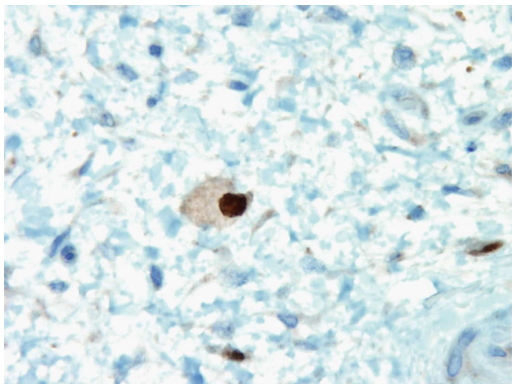

Figure 6 Cell with rhabdomyomatous differentiation were focally positive for myogenin.

esophagus, with the rest originating more distally[5].

Clinically, patients can present with dysphagia for solids and/or liquids, weight loss, intermittent odynophagia, nausea, globus sensation, cough, emesis and retrosternal pain[2]. If proper diagnosis and treatment is not administered, there can be drastic complications such as anemia, vomiting of tumor fragments, oral regurgitation of polyp upon emesis, respiratory compromise and fatal asphyxiation[2,3]. Objective diagnosis can be conducted with barium swallow, esophagogastroduodenoscopy, CT scans, and magnetic resonance imaging (MRI). However, making the diagnosis can require some scrutiny. More specifically, Jakowski and Wakely[3] described a particular case in which the imaging investigations lead to a differential of achalasia initially, later corrected to a giant pedunculated mass. At best, an accurate esophagram can only identify the presence of a mass; often, other examinations must be used in combination to differentiate, evaluate, and grade the tumor. MRI and CT scans are of great help, not only in recognizing the tumor, but also by calculating the fat component of the tumor, hence providing better characterization of the mass: A 100% fat content is in fact consistent with a lipoma, whereas < 75% signifies atypical lipomas or low grade sarcoma[2,7].

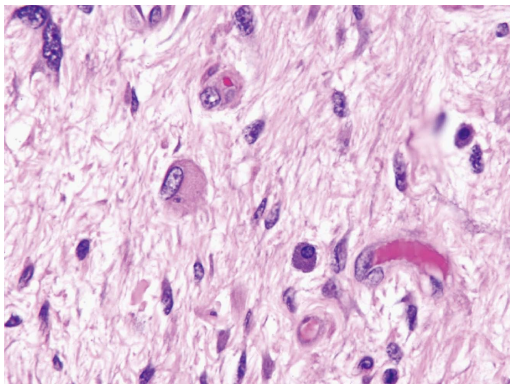

Figure 7 Rabdomyomatous differentiation is characterized by single and loose aggregates of large round cells with abundant eosinophilic cytoplasm.

The standard of care for giant esophageal polyps is surgical resection, which can be directed by different techniques; including an aggressive open cervical approach, radical three-hole esophagectomy, or local endoscopic resection[8,9]. Since in our case the endoscopic ultrasound identified a single proximal stalk without a significant feeding vessel, trans oral endoscopic resection was pursued; making sure completeness was achieved by examining margins of specimen to be uninvolved, as cases of reoccurrence after inadequate resection have been reported[2,5]. Alternatively, resection can also be done through a cervical incision with excision of the polyp from the esophageal lumen, which is in fact the traditional approach, and would have been pursued in presence of a large feeding vessel. Lastly, if the polyps were to have had multiple stalks throughout the entire esophagus, making complete removal through cervical approach unfeasible, an esophagectomy would then be indicated.

In conclusion, given the rarity of the disease, there are only a few studies outlining its optimal management, nevertheless, diagnosis and treatment of this pathology can be approached by customary means, bearing extremely favorable prognosis.

COMMENTS

Case characteristics

A 68-year-old Caucasian male presented with a 2-mo history of worsening intermitted dysphagia, persistent cough, post-prandial retrosternal pain and dull pain on the left side of his neck radiating to his left hear.

Clinical diagnosis

Polypoid mass starting at the level of the upper esophageal sphincter and extending down to the esophagogastric junction, occupying a third of the esophageal lumen.

Differential diagnosis

Neoplastic lesion such as a leiomyoma.

Imaging diagnosis

Esophagogram and computed tomography scan showed a large mass along the

entire course of the thoracic esophagus and an esophagogastroduodenoscopy identified a polypoid mass.

Pathological diagnosis

A 13.0 cm × 6.0 cm × 2.6 cm specimen is identified as a well-differentiated liposarcoma with rhabdomyomatous differentiation arising in a giant fibrovascular polyp and an immunohistochemical stain for MDM-2 supported the diagnosis of liposarcoma.

Treatment

Complete endoscopic resection of the polyp.

Related reports

Esophageal liposarcomas reside in giant fibrovascular polyps and are rare consisting of 0.5% of all esophageal neoplasms. The pathophysiology of esophageal giant fibrovascular polyps is unknown. The only theory with consensus is that an erroneous out-pouching of loose submucosal tissue undergoes traction and peristaltic forces causing it to insidiously grow and elongate into the lumen.

Term explanation

Liposarcoma is a soft tissue neoplasm and is believed to originate from primitive mesenchymal cells rather than mature adipocytes.

Experience and lessons

The standard of care for giant esophageal polyps is surgical resection, which can be directed by different techniques, including a transoral endoscopic resection. A complete resection should be achieved to avoid reoccurrence.

Peer-review

This is only the second case of a rhabdomyomatous well-differentiated esophageal liposarcoma to be reported in literature.

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