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Review Article

Post Imaging Colorectal Cancer: Overview, Risk Factors and Future Directions

Melissa Kyriakos Saad[1], Karam Karam[2], Elias Fiani[3], Charbel Fares[4], Elias Saikaly[5]*

[1]*Saint George Hospital University Medical Center, Beirut, Lebanon*

[2]*Saint George Hospital University Medical Center, Beirut, Lebanon*

[3]*Department of Gastroenterology, Saint George Hospital University Medical Center, Beirut, Lebanon*

[4]*Saint George Hospital University Medical Center, Department of radiology, Beirut, Lebanon*

[5]*Saint George Hospital University Medical Center, Department of General Surgery, Beirut, Lebanon, Saint George University of Beirut, Beirut, Lebanon*

***Corresponding Author:** Elias Saikaly , Saint George Hospital University Medical Center, Department of General Surgery, Beirut, Lebanon, Saint George University of Beirut, Beirut, Lebanon.

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Abstract

Recently there has been an increasing interest towards utilizing noninvasive investigations in screening of colorectal cancer (CRC). To date, Computed Tomography Colonography (CTC) is the only widely available acceptable alternative to colonoscopy. Although CTC is considered to be highly sensitive in detecting colorectal cancer and polyps, it does not provide an absolute protection against missing lesions. This will lead to an entity known as post imaging colorectal cancer (PICRC). Identifying factors contributing to its presence and then attempt to define methods to decrease its incidence will reduce the incidence of PICRC and consequently the incidence of CRC and its associated burden across the globe.

Keywords: Post Imaging; Colorectal Cancer; Directions; Risk Factors

Introduction

Colorectal cancer (CRC) is a common and lethal disease. Genetic and environmental factors contribute to the development of CRC, with different incidence and mortality rates around the world, with geographic differences appearing to be attributable to exposures that are super imposed on background of genetically determined susceptibility. Globally, CRC is the third most commonly diagnosed cancer in males and the second in females, with 1.8 million new cases and almost 861,000 deaths in 2018 according to the World Health Organization. The natural history of colorectal cancer is progression from a small polyp into a larger one, which will progress to dysplasia followed by carcinoma. Progression from adenoma to carcinoma is believed to take an average of at least 10 years [1].

Screening for CRC aids in earlier identification of tumor, hence, earlier stage, which will lead to lower mortality. Furthermore, screening can prevent colorectal cancer by detecting and removing premalignant lesions that will eventually progress to CRC. The recommended screening methods include stool-based testing, endoscopy to visualize the colonic mucosa being it colonoscopy or capsule endoscopy and radiologic imaging to visualize lesions such as Computed Tomography Colonography CTC.

CTC is a noninvasive modality to screen for CRC, whereby endoluminal images of the colorectum are obtained using standard bowel preparation in combination with stool and fluid tagging, mechanical insufflation, and multidetector CT scan. It is considered an option in screening for CRC in asymptomatic patients with average risk of colorectal cancer. Furthermore, it can be utilized to detect proximal synchronous colon cancers in cases where failure to complete a colonoscopy due to an obstructive tumor. Add to this, that it can also be utilized for patients suspected to have colorectal cancer but colonoscopy is contraindicated.

Although CTC is considered to be highly sensitive in detecting colorectal cancer and polyps, it does not provide an absolute protection against missing lesions, just like a colonoscopy. Having said this, an entity known as post imaging colorectal cancer evolved. In fact, missed neoplasia at initial testing probably accounts for more than 50% of post-test colorectal cancers [2]. This review will highlight current knowledge about post imaging colorectal cancer, the common risk factors and the potential solutions to this problem, as those will be critical to reduce the incidence of post imaging colorectal cancer and consequently the incidence of CRC and its associated burden across the globe.

Definition and incidence of PICRC

Defining Post Imaging Colorectal Cancer (PICRC) is varied and complex. It is the preferred term given to cancers appearing after a negative imaging investigation for CRC and appearing beyond 6 months from the date of the initial imaging investigation. There are relatively few studies reporting long-term PICRC rates after CTC [3,4]. A recent systematic review found only 12 studies regarding this topic, reporting on just under 20,000 patients, with a pooled PICRC rate of 4.4% at average follow-up of 3 years [5].

Current knowledge

Although colonoscopy is considered the gold standard for colorectal cancer screening. Interest in noninvasive modalities to screen for CRC is on the rise with Computed Tomography Colonography (CTC) being the only widely available acceptable alternative to colonoscopy. It is being implicated especially in contexts where colonoscopy is contraindicated, or to detect synchronous colon cancer when the colonoscopy can't progress past an obstructed tumor. However, in some instances CTC is being used as screening for CRC in the average risk population. In fact, CTC accounts for more than 15% of all whole-colon testing in England [6] a figure predicted to rise to nearly 20% by 2020 (Anu Obaru 21). When compared to colonoscopy, CTC is equally sensitive for detection of established CRC [7]. Furthermore, Obaro., *et al*. [5]. concluded that the pooled post-imaging colorectal cancer rate was 4·42 percent which is comparable to post colonoscopy colon cancer. The cause of post-imaging colorectal cancers is multifactorial, but in most cases (61%) the culprit lesion was visible in retrospect and potentially detectable [5].

Risk factors leading to PICRC

Tumor biology

There is a growing body of evidence that states that at least a small percentage of PICRC represent a unique subcategory with specific aberrant biology that drives their de novo and rapid growth. It is important to note that the biological environment varies considerably throughout the length of the colon and hence the difference in the biology of proximal versus distal colon cancer. During fetal development for example, the proximal colon originates from the embryonic midgut, whereas the distal colon is derived from the hindgut [8]. Hence, blood supply [8], mucin pH [9] and average crypt length [10] are additional biological features that differ along the colonic tract. Consequently, the environmental and physical properties specific to the proximal colon may contribute to the development of PICRC. On the other hand, prevalence of Microsatellite Instability (MSI), and presence of CpG Island Methylator Phenotype (CIMP) within PICRC is to be determined by future studies, which will lead to better understanding of PICRC and further understand the predilection of PICRC for proximal colon when compared to distal colon.

Surveillance

The optimal time interval for surveillance after a negative CTC remains an area of debate. Bibbins-Domingo., *et al*. [11], concluded that five year interval is recommended in USA. The incidence of PICRC after a negative imaging remains unchanged when comparing 3 year surveillance versus 5 year surveillance. From here, a 5 year interval is a reasonable option for the average risk population. However, in certain subset of patients at higher risk from the general population, a 3 year interval might aid in detecting earlier cancer, further studies are needed in this regard. This highlights the importance of strict adherence to recommended surveillance programs being it by the physicians or the patients to avoid any unjustified increase in the incidence of PICRC.

Radiologist

We believe that centers that have higher case volumes of CTC and more experienced radiologists have higher detection and accuracy for colonic lesions and hence, lower incidence of PICRC. A missed lesion in CTC can be subdivided into ones who failed detection, simply not seen, and ones that failed a correct characterization, a polyp thought to be a colonic fold or retained feces, with the majority of missed polyps being related to errors in detection. In fact, experience and case volume are associated with higher diagnostic sensitivity in some studies, and with higher detection rates in observational studies, meaning it is plausible that PICRC rate is operator-dependent [12,13]. Having said this, striving for perfection in reporting the results of CTC should be the goal. This can be done either by double reading of CTC by two different radiologists, which will increase the cost dramatically and consume manpower, or by implementation of an advanced computer-aided detection (CAD) systems. However, there is a growing evidence that non radiologist can be trained up to an adequate standard whereby they will be able to report the results and act as a second reader [14]. Radiographic technicians performing the CTC studies may be best placed to fulfill this role, providing adequate supervision by a radiologist experienced in CTC. In fact, Fenlon., *et al*. [15] concluded that on average, no difference between trained radiologists and trained technologists was found when reading CTC, however, individual performance was variable and some trainees outperformed some experienced observers. Hence, training should focus heavily on lesion detection, decision making regarding the lesion detected, being it the interval for next imaging or referring for colonoscopy, highlight the importance that readers must spend adequate time reviewing data sets when learning the technique, and possibly include the radiologist detection rate among the quality indicators for CTC.

Size and type of polyps

The natural history of colorectal cancer is progression from a small polyp into a larger one, progressing to dysplasia followed by carcinoma. Progression from adenoma to carcinoma is believed to take an average of at least 10 years [1]. Hence, CRC is considered a preventable disease since most cases arise from precursors that can be detected and removed. Both colonoscopy and CT colonography are highly sensitive for large (≥10 mm) polyps and colorectal cancers, however, colonoscopy better detects diminutive (≤5 mm) adenomas, and serrated polyps. In addition, the increased awareness of serrated lesions being missed and the increased awareness that these lesions has predilection to the proximal colon should lead to increased efforts to detect by CTC and consequently aid in lowering the rate of PICRC. Having said this, and knowing that PICRC has predilection to the proximal colon, we believe that optimizing the proximal colon images should be the goal in future studies and research.

Technical factors

Technical errors do occur. These include scanned volume cannot be adequately evaluated either due to poor colonic distension or retained untagged stool**.** However, with continuous improvements in bowel preparation and colonic distention the results of CTC screening will exceed the expectations and result in a further reduction in the incidence of PICRC, especially those related to the technical errors.

Patient related factors

Some patient related factors contribute to a certain extent in development of PICRC due to inability to obtain a good quality image. For instance, recurrent diverticulitis will result in a fibrotic colon with thickened wall compromising the elasticity of the colon and hence limit colonic distension for optimal CTC leading to increased rate of PICRC. From here, choosing the optimal screening method for the right patient is of paramount importance as this will avoid or decrease the rate of false negative results and consequently the rate of PICRC.

Future Directions

Although significant advances have been made defining and understanding the circumstances around PICRC, more research need to be done to prevent or at least further decrease the rate of PICRC. The keys to reducing the incidence of PICRC is identifying modifiable risk factors for its development and extrapolating from there. Hence, improving the quality of CTC through better colonic preparation, better colonic distention techniques, better reporting of CTC by radiologist through the above-mentioned double reading technique, and better selection of patients will aid in decreasing the rate of PICRC. Furthermore, setting guidelines for radiologists and technologists reading CTC regarding the adenoma or lesion detection rate, time needed to read the CTC and which adenomas should be followed more closely than expected will enhance the role of CTC in preventing CRC and further decrease the rate of PICRC and consequently the incidence of CRC.

Conclusion

The first step towards solving any problem is defining its presence, its scope and factors that lead to its existence. Over the last decade our knowledge about PICRC has increased dramatically. We believe that striving for perfection in CTC reporting is the clue, being it technical related, radiologist related or reader related. Developing the appropriate expertise, with advanced CTC techniques to visualize the colorectum is critical to decrease the incidence of PICRC as well as CRC, and its associated burden across the globe.

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