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The Eternal History: From Intestinal Invagination to Duodenal and Rectal Neoplasia in Lynch Syndrome

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Abstract

Introduction: The clinical presentation of two tumors in Lynch syndrome is rare, it however becomes exceptionally rare when three tumors are diagnosed. Indeed, only very few cases have been described.

Case Presentation: A 42-year-old male came into the emergency room complaining of a non-specific abdominal pain associated with nausea. The radiological and endoscopic evaluation revealed an intestinal subocclusion associated with a rectal and duodenal mass and a polyp originating from the ileocecal valve. The biopsies of the duodenal and rectal lesion resulted in a diagnosis of infiltrating adenocarcinoma of the duodenum and an adenocarcinoma of the middle rectum. Staging was completed and a molecular evaluation showed a heterozygous variant of MSH2 (InSiGHT class 5) compatible with Lynch Syndrome. The patient underwent an ileo-colic resection, a duodenocephalopancreatectomy and a resection of the rectum at three different times. The final diagnosis confirmed the duodenal and rectal neoplasia associated with a high-grade dysplasia on the polypoid lesion. In consideration of the clinical history and diagnosis of Lynch syndrome, the patient was referred for a detailed oncology and genetic evaluation to agree upon the most appropriate oncological treatment and follow-up program.

Conclusions: Triple malignancy in a single patient is very unusual. Its management depends on the stage of the disease. Surgery is the standard of care in localized cancers.

Keywords: Intestinal invagination; Duodenal; Rectal; Neoplasia; Lynch syndrome

Introduction

Lynch Syndrome (LS), or Hereditary Nonpolyposis Colorectal Cancer (HNPCC), is an autosomal dominant genetic syndrome that predisposes individuals to multiple cancer types. Germline mutations in one of the mismatch repair genes, usually MLH1 (human MutL homolog 1), MSH2 (MutS protein homolog 2), MSH6 (MutS protein homolog 6), or PMS2 (PMS protein homolog 2) are known to cause Lynch Syndrome [1,2]. Affected individuals are highly susceptible to colorectal and endometrial cancers, as well as to upper-gastro-intestinal cancers (gastric, duodenum, bile duct and pancreas). The following are emerging as significant causes of death in path_MLH1 carriers, while urinary tract and brain tumors emerge as causes of death in path_MSH2 carriers. Path_MSH6 and path_PMS2 carriers have risks that are so low that when cured from CRC or endometrial cancers any increased risk for other cancers is hardly measurable [1].

The present case report describes a particular presentation of Lynch syndrome and highlights the importance of multidisciplinary approach.

Case Report

Our patient was a 42-year-old male (BMI 21.3). He came into the emergency room complaining of a non-specific abdominal pain associated with nausea. In the first evaluation, no conditions requiring hospitalization were highlighted, no nausea or vomiting. The following day the patient returned to the emergency room showing the same symptoms to which the appearance of vomiting and the alteration of the intestinal tract were added.

The results of first level investigations, which included an abdominal X-Ray (Figure 1) and the specialist's consultation, showed an intestinal subocclusion that required surgery. In addition to fasting and hydration, the patient was referred for medical treatment. Three days later, in order to complete the clinical evaluation, the patient underwent a CT (Figure 2 and 3) scan of the abdomen which confirmed the ileal subocclusion following the thickening of the wall of the last ileal tract as well as the thickening of the II-III duodenal portion and the dilation of the biliary tract. As a result, the patient underwent a gastroscopy which showed a duodenal mass that resulted in partial obstruction of the bowel as well as a colonoscopy (Figure 4 and 5) which showed an ulcerated lesion of the rectum, six centimeters from the anal margin, with the dimension of four centimeters associated with at least three polyps between the rectum and the sigmoid, furthermore an addition ten centimeter polyp, originating from the ileocecal vale and responsible for an intussusception was shown in the right colon. The biopsies of the duodenal and rectal lesion resulted in a diagnosis of infiltrating adenocarcinoma of the duodenum and an adenocarcinoma of the middle rectum. Staging was completed by performing a negative chest CT and a pelvic MRI (Figure 6) which confirmed the presence of polypoid growths in the rectum (T1-T2). A molecular evaluation was also performed on the biopsy samples and it revealed a heterozygous variant of MSH2 (InSiGHT class 5) compatible with Lynch Syndrome.

Following a discussion in a multidisciplinary context, the decision to perform an exploratory intervention, prioritizing the duodenal neoplasia, was taken.

During the exploratory laparotomy an ileocolic resection for intestinal intussusception was performed due to the occlusion which was associated with a biliary and enteric derivation for extemporaneous evidence of peritoneal carcinosis. The definitive histological examination showed a tubulo-villous adenoma with high- and low-grade dysplasia without evidence of neoplasm for the polyp of the ileocecal valve but did not confirm the peritoneal carcinosis. The patient was discharged after thirteen days.

What followed was a chemotherapy protocol with a FOLFOX scheme (six cycles). Six months after the primary operation, the patient underwent further staging with an NMR (Figure 7 and 8), which showed a reduction of the two rectal polyps (cT1-T2 N0) and an abdominal CT scam which showed a reduction of the duodenal mass without biliary duct dilatation. For this reason, the patient underwent a duodenocephalopancreatectomy (DCP) with pancreatic-digiunal anastomosis. He was discharged after eight days. The definitive histological examination showed a poorly differentiated mucinous adenocarcinoma of the duodenum with signet ring cells (ypT3N0).

Three months after the DCP, a new MRI was performed and it showed four polyps between the rectum and sigmoid with dimensional increase of mesorectal lymph nodes. One on the right lateral wall of the rectum by 2 cm (T3b), one on the left posterior-lateral wall of the rectum by 2.5 cm (T3), one at the rectus-sigma passage by 5 mm (T1) and one at the distal sigma by 2.5 cm (T3).

In consideration of this radiological diagnosis, the patient was subject to a segmental resection of the rectum-sigma with Knight-Griffen anastomosis and protective ileostomy. At the patient was hospitalized, awaiting definitive histological examination (Figure 9 and 10). He was discharged after eight days. The definitive histological examination showed an adenocarcinoma of the large intestine in multiple polyposis (pT2 N0 G2-3).

In consideration of the clinical history and diagnosis of Lynch syndrome, the patient was referred for a detailed oncology and genetic evaluation to agree upon the most appropriate oncological treatment and follow-up program.

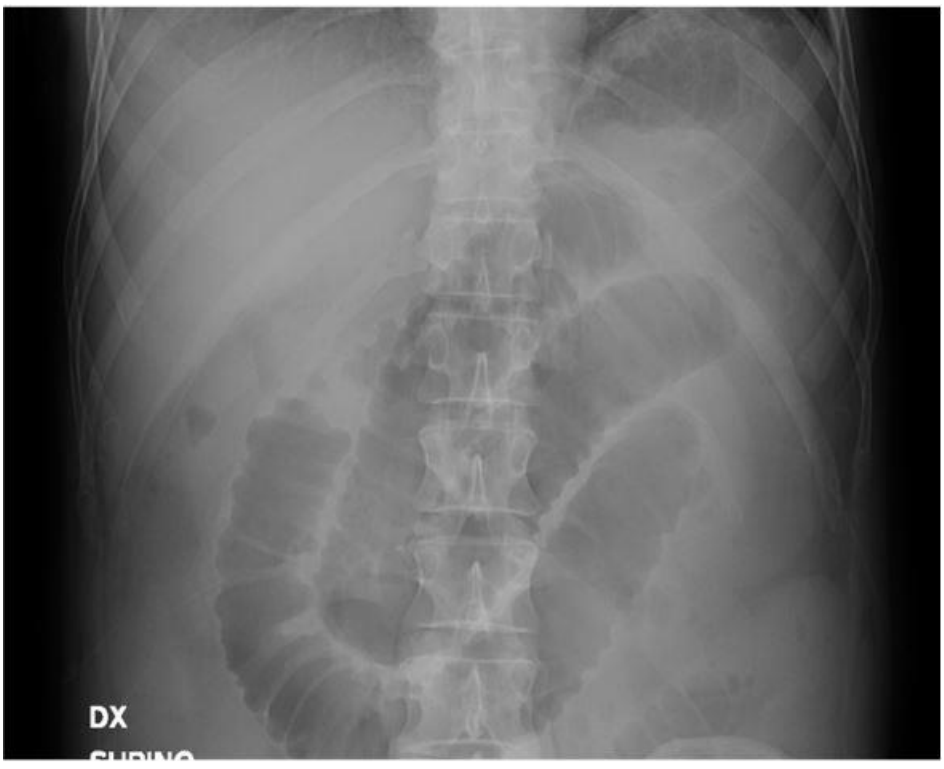

Figure 1: Distension of intestinal loops of the small intestine with multiple levels.

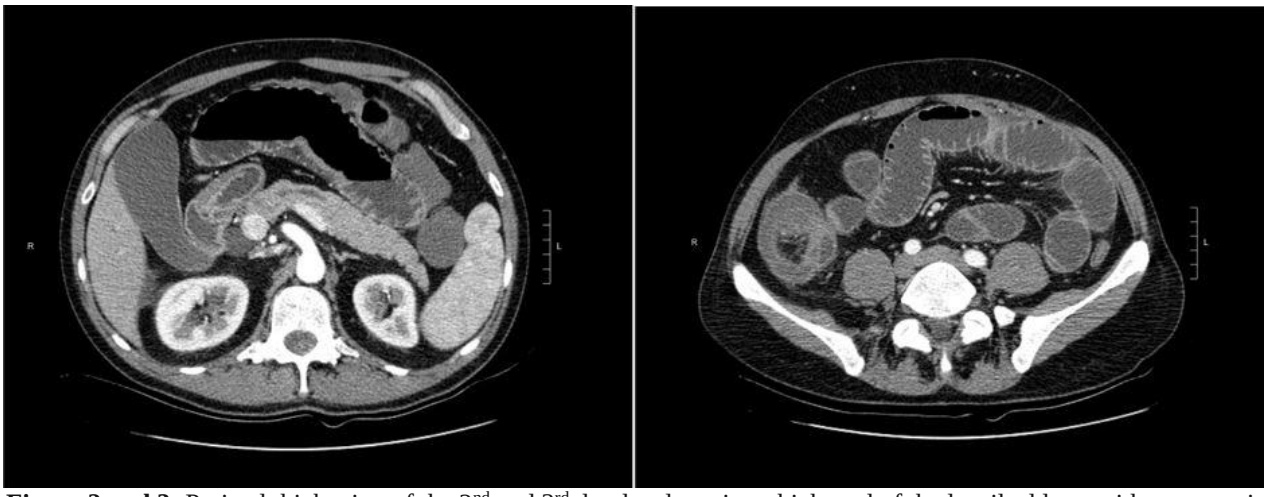

Figure 2 and 3: Parietal thickening of the 2nd and 3rd duodenal portion; thickened of the last ileal loop with mesenteric lymphadenopathies.

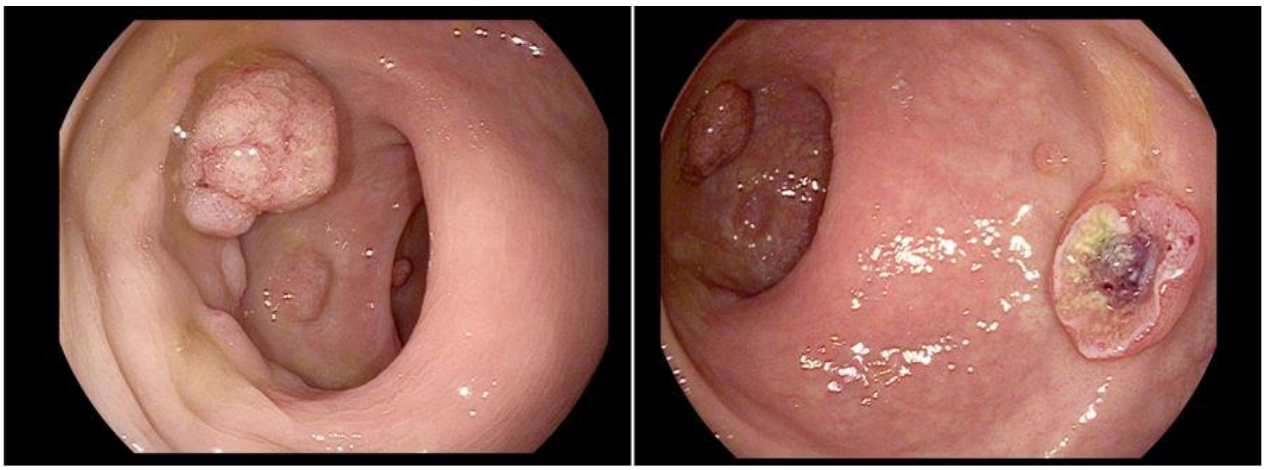

Figure 4 and 5: Polypoid lesions of the rectum-sigma.

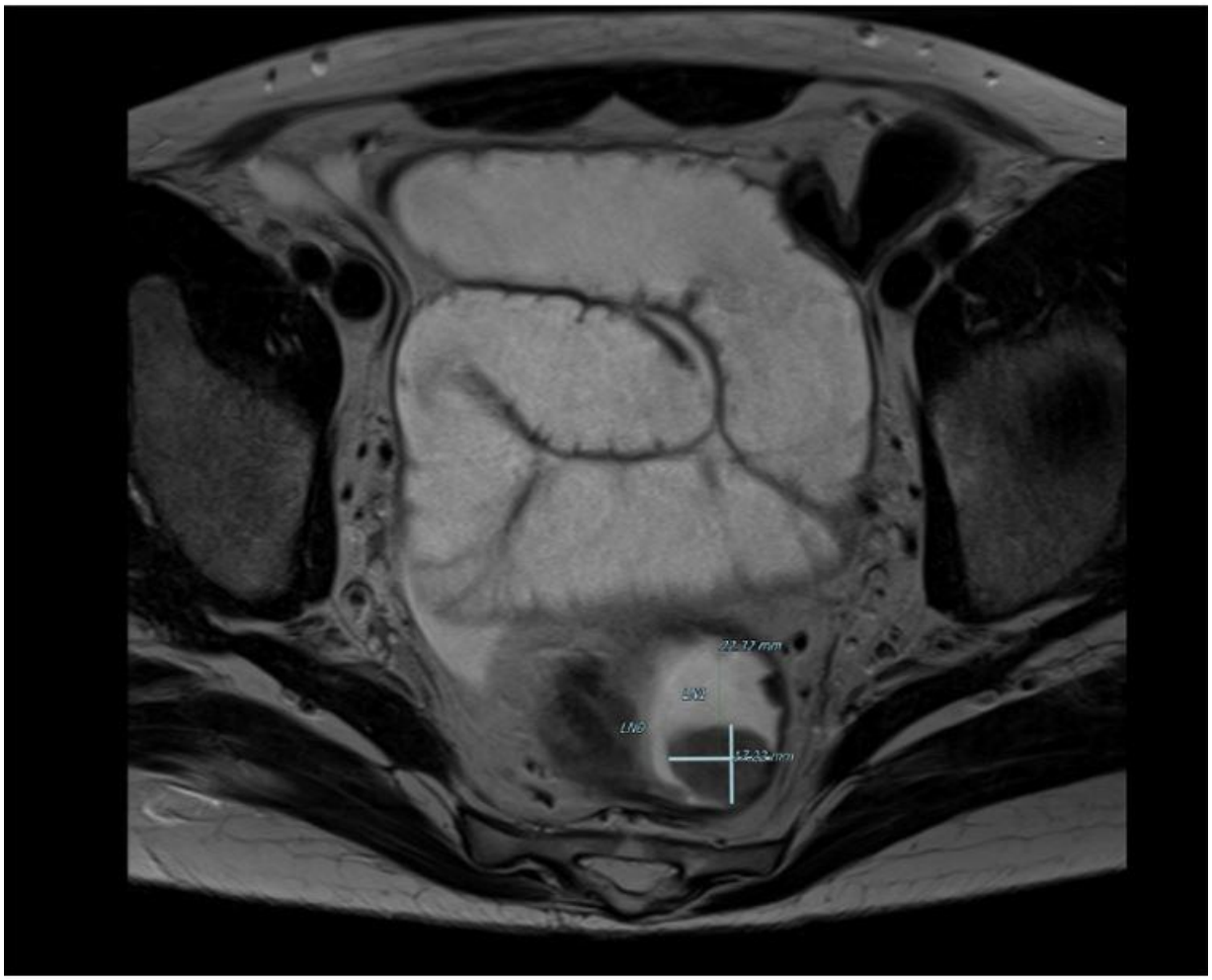

Figure 6: MRI picture of the rectum with T1-T2 lesions.

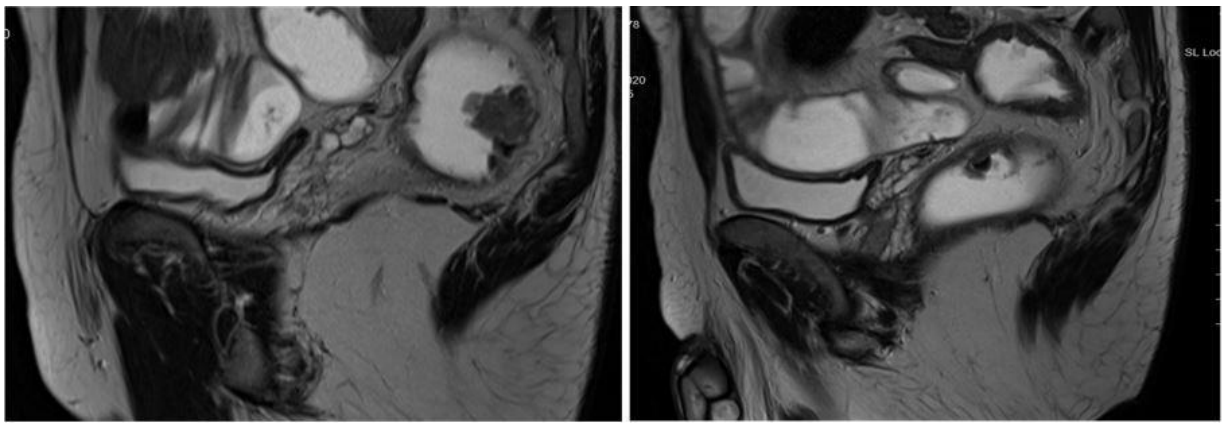

Figure 7 and 8: MRI picture after chemotherapy treatment.

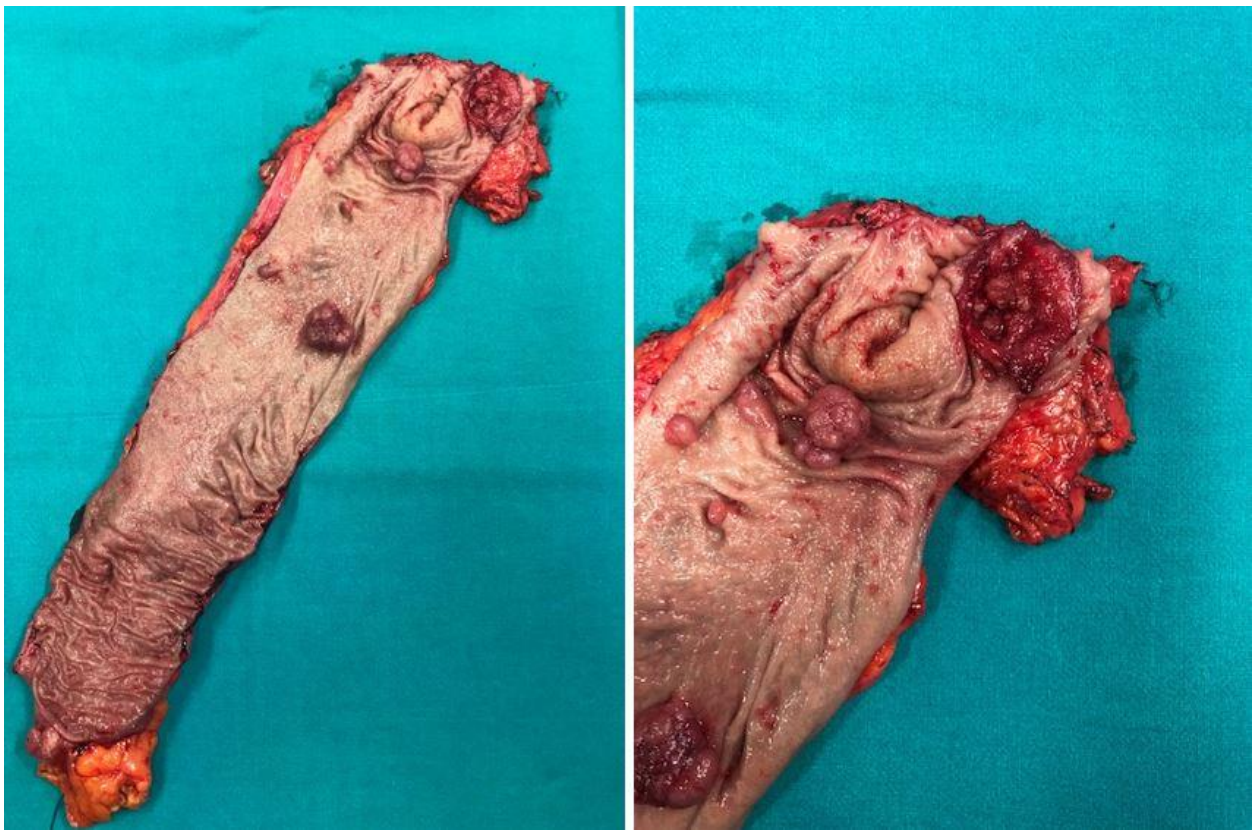

Figure 9 and 10: Specimen of recto-sigma with multiple polypoid formations.

Discussion

There are two categories of multiple primary cancers: synchronous cancers that occur simultaneously or within an interval of six months and metachronous cancers which occur than six months apart [3].

Lynch syndrome is the most common hereditary colorectal cancer syndrome which accounts for 2-4 % of colorectal cancers [4]. This syndrome is associated with an autosomal dominant germline mutation in one of the DNA MMR genes like MLH1 (46,2 to 50 percent), MSH2 (40 to 47,7 percent), MSH6 (6.1 to 10 percent), PMS2 (<5 percent); or the EPCAM gene (1 to 3 percent) [5]. Multiple malignancies are rare and most often involve two sites and the occurrence of the third malignancy is exceptional and occurs in only 0.5% of malignant tumors [6]. In patients suffering from LS syndrome, multiple primary tumors occur in 16% of the cases, of which 4% in the MLH1 mutation and 12% in the MSH 2 mutation [3].

In patients with a diagnosis of LS syndrome, colonoscopy is recommended starting at age twenty – twenty-five or alternatively from two to five years before the earliest diagnosed cancer in a family member. Thereafter a colonoscopy every one to two years following the diagnosis is generally recommended, whatever the mutated gene involved [7,8].

The cumulative risks of Lynch syndrome associated with cancer at the age of fifty and seventy was estimated at around 18-19% and 45-54% respectively, without any significant difference according to sex, with the risks similar for MLH1 and MSH2 mutation and significantly lower for the MSH6 mutation [3].

This difference is also confirmed when analyzing the relationship between genetic mutations and organs affected by the tumor. In fact, with the same mutation, the patient shows a different probably of developing a tumor in a different organ such as an MSH2 mutation that is associated with a different risk of developing a colon, sigmoid/rectum or duodenal cancer (40%, 14% and 2% respectively) [1].

In our case report, the patient was synchronously diagnosed with three distinct primary malignancies, which is a much rarer diagnosis compared to that of two primary cancers, confirming the rarity of the clinical case. The analysis of the genes involved showed a mutation of MSH2, suggesting LS syndrome.

Individuals with Lynch syndrome still end up developing cancer, despite advances in diagnosis and screening. When caught at an early stage, surgical resection represents the mainstay of therapy, with different options such as total abdominal colectomy or segmental resection with follow-up colonoscopy.

The decision to perform one of the different operations is based on the presence of some factors such as age, phenotype and the patient's decision [9].

For this reason, the rate of metachronous cancers after segmental resection or subtotal colectomy has been analyzed. The probability of developing a metachronous tumor in these two cases is approximately 25% vs 8% [10,11]. This risk grows over time, with the incidence of metachronous cancer after the age of thirty being 62% [12].

However, it is not clear whether extensive surgery confers a survival benefit but what is clear is that this approach involves an increased risk of chronic diarrhea and/or incontinence. Therefore, the decision should take into consideration both the patient's risk of additional cancers, surgical risk with additional resection, and patient preferences in accordance to the principle of quality adjusted life years (QALYs) [13,14].

Conclusion

Triple malignancy in a single patient is very unusual. Its management depends on the stage of the disease. Surgery is the standard of care in localized cancers.

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