Synchronous colorectal cancer

Paweł Kozieł, MD, Katarzyna Walkiewicz, MD, Martyna Bednarczyk, MSc, prof. Teresa Kokot, MD, PhD, prof. Małgorzata Muc-Wierzgoń, MD, PhD, Ewa Nowakowska-Zajdel, MD, PhD

Clinical Department of Internal Medicine, Department of Public Health in Bytom, Medical University of Silesia

Specialized Hospital no. 1 in Bytom, Poland

Head of department: prof. Małgorzata Muc-Wierzgoń, MD, PhD

Received: 25.05.2015. Accepted: 21.09.2015.

ABSTRACT

Colorectal cancer is one of the most common neoplasms worldwide. It is still characterized by high mortality and causes ¼ of deaths due to neoplasms. Synchronous cancer is defined as presence of more than one cancer focus (not metastatic) in a patient at the same time. Prevalence of synchronous cancer amounts to 1.1–8.1% of all colorectal carcinomas. More often it affects elderly people and men. Risk factors include inflammatory bowel diseases, hereditary non-polyposis colorectal cancer and familial adenomatous polyposis. Molecular mechanisms underlying the synchronous lesions are: microsatellite instability (MSI), *P53* and *KRAS* mutations as well as glutathione S transferase mutations (GST). In this article, we present a case of a 76-year-old woman with synchronous colorectal cancer in the form of tumors of the sigmoid colon and the ascending colon with metastasis in the liver.

KEY WORDS: colorectal cancer, synchronous cancer, hepatic metastases

Correspondence:
Paweł Kozieł, MD
Clinical Department of Internal Medicine
Department of Public Health in Bytom
Medical University of Silesia
Specialized Hospital no. 1 in Bytom
41-902 Bytom, ul. Stefana Żeromskiego 7
e-mail: pawelko147@wp.pl

INTRODUCTION

Colorectal cancer is one of the most common neoplasms worldwide. It ranks third among cancers in men (after lung and prostate cancer) and second in women (after breast cancer). It is more common in developed countries (about 60% of all cases worldwide) [1]. The highest incidence rate is observed in Australia and New Zealand as well as Western Europe, and the lowest in Africa and South and Central Asia. Colorectal cancer is still characterized by high mortality and causes ¼ of deaths due to neoplasms. Around 600 000 patients die each year [1], and five-year survival concerns barely 60% of patients [2].

In 2010 in Poland, out of 140 500 incidences of cancer, 15 800 cases were colorectal carcinoma. It accounts for about 11.2% of all malignant carcinomas and is the second most common cancer regardless of sex. It also constitutes the second most frequent cause of death due to neoplasm in men and third in women [1].

Synchronous colorectal cancer is defined as presence of more than one primary cancer focus (not metastasis), detected in a patient at the same time (up to 6 months from diagnosis of the first tumor). Metachronous cancer is diagnosed when another primary cancer focus occurs after a certain period of time (more than six months) since the detection of the first one [3].

The criteria for diagnosis of synchronous cancer established by Warren and Gates in 1932 are as follows:

1. each tumor must comply with histopathological criteria for malignancy
2. each tumor must be separate
3. none of the tumors is a metastasis
4. synchronous cancers must be diagnosed at the same time (e.g. during one examination) or up to six months after the first diagnosis [4, 5].

Data from various studies indicate that synchronous cancers account for 1.1–8.1% of the total number of colorectal cancers [3]. Such a wide range may result from the lack of clear-cut differentiation of synchronous and metachronous cancers. Some authors did not take the aforementioned criteria into consideration and established a longer time to diagnose the second tumor (up to 12 months), thus including in the group with synchronous cancers a greater number of patients [3].

A higher risk of synchronous tumors is observed in elderly patients, over 75 years of age [6]. As in the case of isolated colon cancer, men fall ill more often than women (1.8 : 1 ratio) [6]. Some observations also indicate that synchronous changes have a greater propensity to metastasize, which simultaneously worsens the prognosis [7]. Most often, 2 synchronous changes are detected but there was a case of a patient with 7 synchronous tumors in the colon [8] and a trifocal colorectal cancer with liver metastases in the course of Lynch syndrome [9].

Risk factors of synchronous cancer include non-specific inflammatory bowel diseases, hereditary non-polyposis colorectal cancer (HNPCC) and familial adenomatous polyposis (FAP) [3]. Improper diet (low fiber and high animal fat content) and low physical activity (regular physical activity reduces the risk of cancer by as much as 40–50%) are considered significant environmental risk factors of colorectal cancer [10] whereas excessive alcohol consumption may prompt the creation of synchronous changes. In one study, it was demonstrated that patients who consumed alcohol regularly over many years run a 6.8 times bigger risk of synchronous colorectal cancer than patients who do not drink alcohol [11].

Compared with isolated tumors, synchronous cancers are mostly located in the proximal part of the colon, which may be connected with a higher incidence of hereditary pathologies (HNPCC and FAP) that predispose patients to synchronous changes. It is observed that synchronous cancer, more often than single changes, coexists with benign gastrointestinal adenomas [12].

Just as in an isolated colon cancer, molecular basis of synchronous changes is seen in microsatellite instability (MSI), *P53* and *Kras* mutations and most recently, increasing importance is attributed to mutations of glutathione S transferase (GST) [3]. Japanese researchers conducted molecular analysis of synchronous and sporadic cancers, comparing synchronous colorectal cancers (47 patients) and isolated ones (2021 patients). They observed a significantly worse prognosis in patients from the first group and important molecular differences between these two types of cancers. The synchronous tumors were more likely to demonstrate microsatellite instability, presence of *BRAF* mutation and phenotype of methylated CpG islands (frequent CpG island methylation – CIMP-high) [13]. CIMP-high phenotype correlates with increased risk of colon cancer and is associated with methylation of a variety of genes whose silencing may play a role in the pathway leading to neoplasia (*MLH1*, *P16*, *IGFBP-7*) [14].

Synchronous cancer diagnosis can be difficult. Colonoscopy does not always allow for visualization of changes, because of a too small size of the tumor or poor preparation for the ex-

amination. Similarly, intraoperative palpation of the colon may not be sufficient. It is estimated that approximately 50% of synchronous tumors are not detected [15], which was confirmed by prospective studies conducted by Langevin and Nivatvongsa in 1984. [16]. Better results were obtained by Nikoloudis et al. in a study of 283 patients (including only 6 patients diagnosed with synchronous cancer) operated for colorectal cancer. Diagnosis of multiple tumor using traditional diagnostic methods (colonoscopy and dual-contrast imaging of the lower part of the gastrointestinal tract) was correct in 66.6% of the cases [17].

Helpful in the diagnosis may be the use of virtual colonoscopy using CT [18]. Unfortunately, also this method has its limitations because it is difficult to differentiate advanced adenoma from carcinoma [3].

CASE PRESENTATION

A 76-year-old woman was referred to the department of internal medicine because of increasing weakness, anorexia and weight loss. Laboratory tests showed moderate anemia, iron deficiency, hypoalbuminemia, and elevated levels of tumor markers – CEA (91.7 ng/ml) and CA19-9 (262 U/ml). Ultrasonography of the abdominal cavity revealed the presence of numerous, well demarcated from normal parenchyma, heterogeneous changes in the liver, whose image initially suggested metastatic changes.

During hospitalization, gastroscopy and colonoscopy were performed. CT scan of the abdominal cavity was also made, which showed numerous liver metastases, intraperitoneal lymphadenopathy and thickening of the wall of the descending colon with infiltration of the adipose tissue in that area. Colonoscopy revealed two tumors which resembled synchronous colorectal cancer. The first tumor, covered in necrotic tissues, brittle and bleeding during test, was located in the sigmoid colon. It infiltrated the intestinal wall and significantly occluded the lumen of the colon. The second tumor, with similar morphology, was located in the ascending colon. Numerous samples of the lesions were taken for histopathological examination. Endoscopic image of the tumors suggested the presence of synchronous colorectal cancer, which was confirmed by a pathologist (*adenocarcinoma necroticans* in both lesions).

After oncological consultation, the patient was referred to palliative surgery because of possible risk of obstruction or bleeding from the gastrointestinal tract.

The surgery started with a midline incision of the peritoneal cavity of the patient (after anesthesia). Both lobes of the liver were changed by metastases, the biopsy was performed on the left one. Small intestine was infiltrated by the lesion in the cecum area. Right-sided colon was resected. The tumor occluded the lumen of the intestine in the sigmoid colon area, so the latter was also resected.

The histopathological examination revealed:

1. Polypoid sigmoid colon tumor with a broad base – G2 *adenocarcinoma* with focal perineural invasion and microangioinvasion. One lymph node without neoplastic infiltration was found.
2. Polypoid infiltration in the ascending colon – G3 *adenocarcinoma partim mucinosum*, with cancer tissue around the nerves and vessels, visible angioinvasion. Eight lymph nodes were found, out of which 6 contained neoplastic infiltration and focal neoplasm in perinodal adipose tissue.
3. *Adenocarcinoma metastaticum* in the liver sample.

Because of poor general condition (level 3 on the Zubrod scale), the patient did not qualify for palliative systemic therapy. She was recommended symptomatic treatment under control of a GP and home hospice.

DISCUSSION

Synchronous colorectal cancer is rarely diagnosed and is not the most common clinical problem. Therapeutic approach depends on the location and advancement of the cancer, the patient's clinical condition as well as concomitant diseases, obstruction or gastrointestinal bleeding risk and the expected survival time [19, 20]. If the changes are located in the colon, surgery is recommended in the first place. If the changes coexist with rectal cancer, preoperative radiotherapy or chemoradiotherapy should be considered.

Liver metastases occur in about half of patients treated radically for colorectal cancer. Simultaneous colorectal cancer and liver metastases is observed in about 25% of patients [20]. However, there are no clear rules as how to manage synchronously detected metastatic lesions. The treatment strategy should be determined by a multidisciplinary team composed of a pathologist, a surgeon, a radiation oncologist, and a clinical oncologist. The assessment of resectability of the metastases is important because surgical removal of the changes leads to long-term overall survival.

Currently, there are several strategies considered. The "classical" one consists in removal of the primary colon tumor, followed by chemotherapy (and radiotherapy in the case of rectal cancer) and resection of the liver lesions within 3–6 months after surgery of the primary tumor.

It is also possible to qualify a patient for a simultaneous removal of the primary tumor and metastatic lesions in the liver, but this only applies to patients not requiring complex surgery.

Nevertheless, such an approach is impossible in the majority of cases due to the complexity of the operation and other factors dependent on the patient. Removal of the primary tumor and the metastases in the liver, preceded by a systemic treatment based on multi-drug regimens, and even the combination therapy of molecularly targeted drugs, is another strategy. If the liver metastases are resectable and there is no risk of obstruction or bleeding, metastatic changes can be removed, followed by adjuvant chemotherapy and qualification for surgery of the primary tumor. There is also a possibility of introducing neoadjuvant chemotherapy and, once the resectability of the changes is assessed, performing the surgical removal of the metastases with postponement of the primary tumor resection. While determining the therapeutic management, one should take only those strategies into account that offer the greatest chances of obtaining a radical resection [21].

In the neoadjuvant or adjuvant therapy regimens containing 5-fluorouracil, oxaliplatin, and irinotecan are most often prescribed. In Poland, molecularly targeted drugs are available only in the palliative treatment of patients with inoperable cancers. In the second-line treatment, patients meeting the criteria for the drug program can take bevacizumab with FOLFOX regimen, and in the third-line treatment, depending on the status of the *KRAS* and *RAS* genes – cetuximab or panitumumab in monotherapy. In targeted therapy for metastatic colorectal cancer, new drugs were used, for which no predictive factors have been established so far (similarly to bevacizumab). These are: aflibercept and regorafenib, neither of which is available in Poland [20, 22].

Search for predictive factors of new drugs that modify the signaling pathway leading to disease progression appears to be a valid subject of research aimed at improving the individualization of treatment and survival of patients with advanced and chronic malignancies [23].

Some local treatment methods can be used when there is no possibility of surgical removal, such as: stereotactic radiotherapy, termoablation, embolistation, radioembolistaion and kriotherapy, independently of or alternatively to the systemic therapy [20].

CONCLUSIONS

Thanks to local methods of treatment, introduction of new therapeutic strategies using new drugs as well as more and more aggressive surgical treatment, it was possible to reach significant improvement in survival of patients with colorectal cancer in the 4th clinical stage, even up to 30 months.

In contrast, a high probability of overlooking synchronous changes in the diagnostic process and increased aggressiveness of synchronous colorectal cancer cause inadequate treatment and lead to more frequent therapeutic failures.

Acknowledgements

Authors report no conflict of interest.

References

1. Krajowy Rejestr Nowotworów (KRN, National Cancer Registry) [online: http://onkologia.org.pl/]. Access: April 2015.
2. Ferlay J, Steliarova-Foucher E, Lortet-Tieulent J et al. Cancer incidence and mortality patterns in Europe: estimates for 40 countries in 2012. Eur J Cancer 2013; 49: 1374-1403.
3. King-Yin Lam A, Sze-Yan Chan S, Leung M. Synchronous colorectal cancer: Clinical, pathological and molecular implications. World J Gastroenterol 2014; 20(22): 6815-6820.
4. Yang J, Peng JY, Chen W. Synchronous colorectal cancer: Clinical, pathological and molecular implications. Dig Surg 2011; 28: 379-385.
5. Kluciński A, Pawłowski W, Krasnodębski IW. Opis przypadku. Guzy synchroniczne jelit – współwystępowanie gruczolakoraka poprzecznicy i rakowiaka jelita cienkiego. Przegl Gastroenterol 2006; 1(3): 126-128.
6. Latournerie M, Jooste V, Cottet V et al. Epidemiology and prognosis of synchronous colorectal cancers. Br J Surg 2008; 95: 1528-1533.
7. Mulder SA, Kranse R, Damhuis RA. Prevalence and prognosis of synchronous colorectal cancer: A Dutch population-based study. Cancer Epidemiology 2011; 35(5): 442-447.
8. Kaibara N, Koga S, Jinnai D. Synchronous and metachronous malignancies of the colon and rectum in Japan with special reference to a coexisting early cancer. Cancer 1984; 54: 1870-1874.

9. Mąka B, Roman P, Kurek A et al. Rzadka postać zespołu Lyncha z trzema synchronicznymi, o podobnym zaawansowaniu, ogniskami gruczolakoraka okrężnicy. Chirurgia Polska 2013; 15(1): 88-92.
10. Litwiniuk M, Kara I. Physical activity and cancer. OncoReview 2012; 2(4): 228-233.
11. Maekawa SJ, Aoyama N, Shirasaka D et al. Excessive alcohol intake enhances the development of synchronous cancerous lesion in colorectal cancer patients. Int J Colorectal Dis 2004; 19: 171-175.
12. Chen HS, Sheen-Chen SM. Synchronous and "early" metachronous colorectal adenocarcinoma: analysis of prognosis and current trends. Dis Colon Rectum 2000; 43(8): 1093-1099.
13. Katsuhiko N, Shoko K, Natsumi I et al. A prospective cohort study shows unique epigenetic, genetic, and prognostic features of synchronous colorectal cancers. Gastroenterology 2009; 137(5): 1609-1620.
14. Fernando WC, Miranda MS, Worthley DL et al. The CIMP phenotype in BRAF mutant serrated polyps from a prospective colonoscopy patient cohort. Gastroenterol Res Pract 2014; 2014: ID 374926.
15. Arenas RB, Fichera A, Mhoon D, Michelassi F. Incidence and therapeutic implications of synchronous colonic pathology in colorectal adenocarcinoma. Surgery 1997; 122(4): 706-710.
16. Langevin JM, Nivatvongs S. The true incidence of synchronous cancer of the large bowel. Am J Surg 1984; 147(3): 330-333.
17. Nikoloudis N, Saliangas K, Economou A et al. Synchronous colorectal cancer. Tech Coloproctol 2004; 8(1): 177-179.
18. Lebda-Wyborny T, Barczyk A, Pilch-Kowalczyk J. Wirtualna kolonoskopia CT – nowa metoda oceny patologii jelita grubego. Chirurgia Polska 2008; 10(2): 88-100.
19. Krzakowski M, Warzocha K (ed.). Zalecenia postępowania diagnostyczno-terapeutycznego w nowotworach złośliwych. VM Media, Gdańsk 2013.
20. Van Cutsem E, Cervantes A, Nordlinger B et al. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol 2014; 25(suppl. 3): iii1-iii9.
21. Ihnat P, Vavra P, Zonca P. Treatment strategies for colorectal carcinoma with synchronous liver metastases: Which way to go? World J Gastroenterol 2015; 21(22): 7014-7021.
22. Van Cutsem E, Tabernero J, Lakomy R et al. Addition of aflibercept to fluorouracil, leucovorin, and irinotecan improves survival in a phase III randomized trial in patients with metastatic colorectal cancer previously treated with an oxaliplatin-based regimen. J Clin Oncol 2012; 30(28): 3499-3506.
23. Muc-Wierzgoń M, Nowakowska-Zajdel E, Dzięgielewska-Gęsiak S et al. Specific metabolic biomarkers as risk and prognostic factors in colorectal cancer. World J Gastroenterol 2014; 20(29): 9759-9774.

Authors' contributions:
Paweł Kozieł – idea, collection of references
Katarzyna Walkiewicz – collection and analysis of references
Martyna Bednarczyk – preparation of the case study
Teresa Kokot – idea, translation
Małgorzata Muc-Wierzgoń – idea, collection of references
Ewa Nowakowska-Zajdel – idea, translation, analysis of the case study.