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Benefits in the Progression of Colorectal Cancer with Screening Methods and Treatment Based on Molecular Tests

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1. Summary

1.1. Abstract

Rectal cancer is the third leading cancer in the world in terms of incidence and mortality according to GLOBOCCAN. The prognosis of the disease varies according to the stage, being better in the early stages and worse in the advanced and metastatic stages. Early diagnosis of colorectal cancer made through screening programs is accompanied by an improvement in the cancer progression. The introduction of colonoscopy examinations and testing for blood clots has made it possible to diagnose precancerous lesions and colorectal cancer in the early stages when the survival rate is better [1]. The treatment of colorectal cancer has evolved from just surgery before the 1980s to chemotherapy and radiotherapy in the 1980s and improving in later years with the introduction of new cytotoxic drugs that have improved survival. [2]. With advances in molecular biology methods, it is possible introduction as part of the treatment of new targeting and immunomodulatory drugs based on the results of these molecular tests.

Treatment with these drugs has brought an improvement in the course of the disease of patients with colorectal cancer. [3].

1.2. Conclusion: The strategy for treatment for CRC should be assessed with respect to its effectiveness, sensitivity, the number of false positive results, safety, and comfort. Furthermore, the cost and economic factors pertaining to the screening programs should be observed in order to help patients with decision making, and the prevailing clinical policies should be taken into consideration.

2. Introduction

Colorectal cancer (CRC) is the third most common cancer in the world and the second leading cause of death according to GLOBOCCAN 2020. The number of new cases is estimated at 1.9 million cases worldwide and a mortality rate of 0.9 million cases. There is an increasing trend in the number of new cases that can be attributed to some extent to the western style of nutrition, is rich in red meat and fats and poor in fruits and vegetables. According to GLOBOCCAN 2020 the incidence for Albania is 387 patients and colorectal cancer mortality is 3.8%.

2.1. History of colorectal cancer screening

Today's interest in doing colorectal cancer screening has its beginnings in a London hospital and in an internship office in Ohio. It was demonstrated that colorectal cancer did not occur de-nuovo, but from the transformation of a premalignant polyp and if caught at an earlier stage survival would be better. It was therefore best for colorectal cancer to be detected as early as possible by screening methods. Before fiber optic colonoscopy was available, examination of the cervix was based on visualization of the barium enema colon and if polyps were to be removed, they could be surgically removed. Innovations in technology made it possible to improve colonoscopy techniques and it was possible to see the colony from the inside and remove the polyps. Years later the introduction of colonoscopy created the opportunity to do studies (trials) that showed that these concepts were true. Since colorectal cancer is characterized by a gradual transition from adenoma to carcinoma screening, it is logical to perform colorectal cancer. The time it takes for an adenoma to turn into cancer is not known for sure, but

evidence shows that it is not less than 10 years and can vary from 10-15 years [4, 5]. In the 1990s, the benefits of screening began to become more apparent with randomized trials of Mandel and colleagues, Hardcastle, and Kronborg, who showed a 15-33% reduction in colorectal cancer mortality only from fecal occult blood tests [6, 7, 8].

In 2013, a 30-year study by the Minnesota Colon Cancer Control Study showed a 32% reduction in mortality [9]. The three most widely accepted methods of screening are fecal occult blood test (FOBT), colonoscopy and sigmoidoscopy. Using the FOBT test in Albania, as part of the check-up programs, we have noticed a number of cases diagnosed at various stages, mainly the without lymph nodes T2N0M0 and T3N0M0.

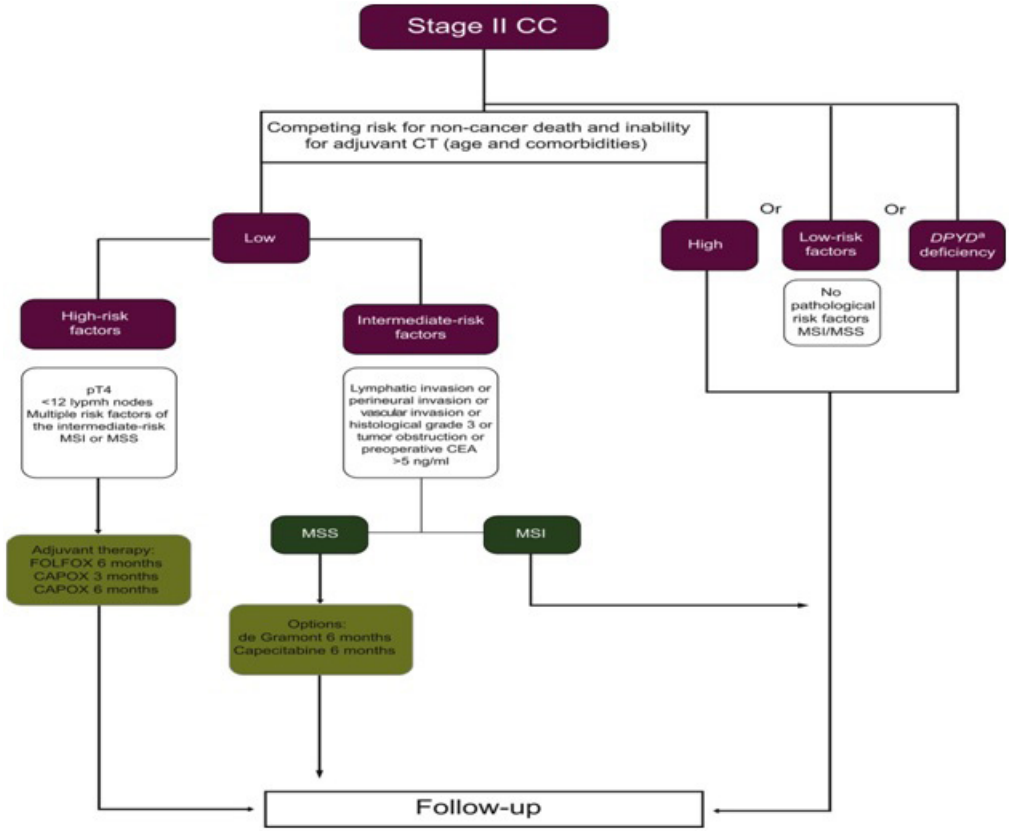

Figure 1: Treatment algorithm in stage II colon cancer (CC).

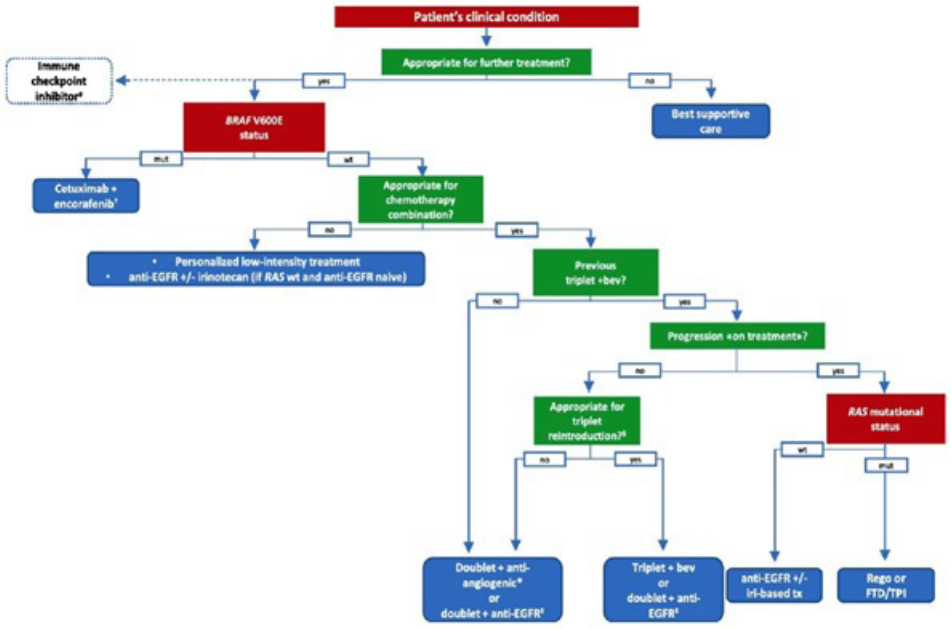

Figure 2: Algorithm for the treatment of metastatic colorectal cancer.

2.2. Progression of colorectal cancer during the years 1970-2010 [5]

Years 1970. In the years 1970- 1980 began the introduction of examinations sigmoidoscopy and flexible colonoscopy. Possible cancer was detected in precancerous polyps and colorectal cancer surgically curable.

Years 1980. 1885 Chemotherapy and radiotherapy after surgery become standard post-combination treatment shown to improve the survival of patients with rectal cancer. Prior to the mid-1980s, patients with rectal cancer underwent surgery alone, resulting in a high percentage of pelvic relapses resulting in morbidity and death.

A large-scale study by the Netherlands showed that patients undergoing preoperative radiotherapy had fewer pelvic relapses compared to those undergoing those who did total meso-rectal resection only [10].

Later the German Rectal Study showed that radiotherapy or adjuvant chemotherapy improved the control of the blood better and more likely to preserve the sphincter than it was applied after surgery [11].

Based on these studies, a standard of treatment was set in Europe and the United States.

Years 1990-The first tests were performed to detect genetic abnormalities associated with colon cancer, polyposis, familial adenomatous cancer, and Hereditary nonpolyposis colorectal cancer (HNPCC). These tests made it possible for people at high risk to be identified and followed closely. Since the end of the year, we have been better acquainted with HNPCC as an autosomal dominant disorder with an inherited tendency to develop rectal cancer in the absence of colon polyps. The incidence of HNPCC is estimated at 4-6% of all colorectal cancer cases, while about 70% are sporadic and about 25% are familial cancers caused by hereditary mutations, but not all of them are classified as hereditary cancers because they do not cause cancer. The leading cause of HNPCC is now Lynch syndrome, which is caused by mutations inherited in the alleles that encode AND for repair proteins such as MSH2, MLH1, MLH6, PMS1 and PMS2 [12]. It is already known that mutations in specific genes can lead to colorectal cancer as they can occur in many other types of cancer. 1991-Chemotherapy with 5-fluorouracil given after surgery showed an improvement in survival in patients with colon cancer. The improvement in survival at 7 years was 17% [13]. 1996-Irinotecan became the first approved agent in 40 years for advanced colorectal cancer [14].

Years 2000

2002-Oxaliplatin combined with 5-Fluoururacil and leucovorin (together in the protocol called FOLFOX) was approved to treat advanced colon cancer [15].

2004-FOLFOX was initially approved as a therapy for advanced cancer. It was later approved at an earlier stage after surgery, as a pivotal study found that it increased the time a patient suffered without recurrence of the disease (MOSAIC study) [16].

2004-Bevacizumab (Avastin), when combined with FDA-approved chemotherapy to treat advanced colorectal cancer, becoming the first approved antiangiogenic therapy. This medicine blocks the blood vessels that feed the tumor [17].

2004, 2006 -Targeted therapy with cetuximab and panitumumab were approved for the treatment of metastatic colon cancer [18]. 2005 – Evidence of Capecitabine use is an oral formulation of 5-Fluorouracil approved for the treatment of colorectal cancer [19].

2007-Studies showed that patients who adhered to a low-fat diet and exercise regularly had a lower postoperative risk for early-stage disease, indicating that lifestyle factors had a significant effect on the risk of recurrence [20].

2008 Studies showed that targeted therapies with cetuximab and panitumumab are effective only in patients with normal K-RAS gene form (mutation-free K-RAS) helping to personalize treatment while avoiding unnecessary treatments and treatment costs [21].

2.3. Recent news in the diagnosis and treatment of colorectal cancer

Ever since the Moertel study in 1990 showed an increase in survival when cancer patients were treated with adjuvant chemotherapy compared to chemotherapy alone especially in the third stage of the disease [22, 23] and then the MOSAIC study showed that the addition of oxaliplatin 5-Fluorouracil-leucovorines was associated with a benefit compared to only 5 FU / leucovorin, adjuvant treatment with fluropyrimidine + - leucovorin stabilized as standard adjuvant therapy in stage III and in high-risk patients in stage II [24]. Although there has not been much innovation in adjuvant treatment at the localized stage, we can say that even in these stages of the disease progress has been made thanks to the discovery of biomarkers that help in a more accurate diagnosis and provide an aid in placement of treatment. Molecular testing is more specific compared to other examinations and allows the clinician for a more personalized treatment of the colorectal cancer patient. The most widely used biomarkers in colorectal cancer are MSI and K-RAS mutations in tumor tissue, in order to better classify the tumor, make the prognosis of the disease, and administer therapy [25]. While the role of MSI is that at the moment when you have to decide whether or not the patient should receive adjuvant therapy, but also in cases of colorectal cancer with metastases to benefit or not from immunotherapy, K-RAS as an influential factor in determining the type of therapy is only in the metastatic stage of the disease [25]. In the localized stages of the disease there have not been many changes in terms of the range of drugs used, the role of biomarkers remains more decisive whether or not the patient will undergo adjuvant treatment, whereas in the metastatic stage the role of biomarkers detected through biology molecular is clearer [25]. CAPOX, capecitabine and oxaliplatin; CEA, carcinoembry-

onic antigen; CT, chemotherapy; MSI, microsatellite instability; MSS, microsatellite stability. a If partial but not complete DPYD deficiency, with uracilemia >16 ng/ml, discuss each patient case individually depending on the benefit/risk balance for adjuvant fluoropyrimidine [26].

Treatment of colorectal cancer involves a multimodal approach based on tumor characteristics (eg number and localization of metastases, tumor progression, presence or absence of biomarkers, etc.) and patient-related factors (eg comorbidity, prognosis, etc.). In the metastatic stage systemic treatment is mainly the main treatment, but patients with metastatic colorectal cancer should be evaluated by multidisciplinary staff, because during the course of treatment patients may undergo surgery as a result of, for example, obstruction or hemorrhage, and should be evaluated if, in addition to the removal of the primary tumor, they should be evaluated for metastasectomy when the criteria are met [26]. Patients with metastatic but potentially vulnerable disease may initially initiate induction chemotherapy treatment with two or three cytotoxic drugs that can be combined with an anti-EGF or anti-EGFR in K-RAS wilde type patients and later evaluated resilience [27]. The most common first-line treatment in patients with treatment metastases is usually a fluoropyridine combined or not with oxaliplatin and / or irinotecan with or without a targeted biological therapy [28]. The second line treatment will be based on what was the first line therapy, how is the organ reserve and was it refractory to the first line. Usually if the first line therapy has been with irinotecan, the second line therapy can be FOLFOX or CapeOX and if the first line therapy has been FOLFOX or CapeOX the second line treatment will be irinotecan monotherapy or FOLFIRI [29]. The duration of treatment is judged according to each case. It can be from 3-6 months followed by maintenance therapy for several months or maintenance therapy until progress [30-31].

Metastatic colorectal cancer remains incurable in most cases, but survival is enhanced by advances in systemic chemotherapy especially when targeting agents such as anti-VGEF and anti-EGFR monoclonal antibodies are added [30-31]. First-line therapy is a key moment for the effectiveness of treatment and should be carefully selected after considering both clinical factors and biological markers, especially RAS and BRAF [32].

According to the recommendations of ESMOS and NCCN at the time of diagnosis of metastatic cancer testing for K-RAS and B-should also be done [31].

Among the antiangiogenic therapies used are the bevacizumab monoclonal antibody that targets anti-VEGF-A and the recombinant Aflibercept protein fusion that blocks VEGF-A, VEGF-B, and placental growth factor. with lack of K-RAS mutation [30-31]. Standard therapies for colorectal cancer have been chemotherapy, surgery and radiotherapy which can be used in combination to treat patients. However most patients relapse even after a series of treatments. So it is important to find alternative treatment options to treat patients with CRC [32]. Another new therapeutic alternative in colorectal cancer is immunotherapy. Preclinical and clinical investigations of immunotherapy include immunocheckpoint inhibitor (ICI) blockade that looks promising, yet the effectiveness of ICI treatment is influenced by microsatellite instability (MSI) in each of the CRC patients [33]. MSI status is determined by immunohistochemical staining and polymerase chain reaction targeting 5 MSI markers targeting 5 MSI markers of BAT25, BAT26, D2S123, D5S346, and D17S250. Patients with CRC are divided into three groups based on the mutated structure of MSI-High microsatellite instability (MSI-H), MSI-L low microsatellite instability, stable MSS microstability. [33]. Evidence that dMMR / MSI patient status is an important predictive marker for ICI immunotherapy treatment in CRC is increasing [33]. Researchers have found that cases with dMMR / MSI-H respond better to immunotherapy than those with MSS. 12. ICI drugs targeting PD-1 and CTLA4 are more potent in metastatic cancer with MSI_H due to higher mutational load (tumor burden mutation TMB). High TMB is harvested with the highest neoantigenic load thus increasing immunogenicity [34, 35, 36]. However, not all MSI-H patients benefit from treatment with an immuno-checkpoint inhibitor. About 95% of patients are pMMR / MSS. These facts underscore the need to find more reliable predictive biomarkers for ICI [37,38].

In addition to the already standard therapies for colorectal cancer, new alternative therapies are being studied with the aim of increasing the effectiveness of treatment and reducing side effects as well as reducing the risk of secondary tumors. In terms of drug treatment of colorectal cancer, we can say that in most cases in Albania we implement the recommendations for adjuvant treatment. This is also due to the better pathological staging with already more complete data as after European standards, but there is still room for improvement, as in most cases of the stage without metastases in lymph nodes where adjuvant treatment is debatable. microsatellite instability information was missing. In the metastatic stage of CRC cancer in Albania there is still much room for improvement in both diagnosis and treatment. Personalized therapy based on molecular testing is performed in only a small number of patients who provide it privately and the only targeted therapy in the hospital is antiangiogenic therapy with Bevacizumab. It remains a challenge for medical staff to implement new diagnostic methods and molecular tests and to establish personalized treatment based on molecular test results.

3. Conclusion

The strategy for treatment for CRC should be assessed with respect to its effectiveness, sensitivity, the number of false positive results, safety, and comfort. Furthermore, the cost and economic factors pertaining to the screening programs should be observed in order to help patients with decision making, and the prevailing clinical policies should be taken into consideration.

4. COI Statement

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5. Disclosure

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References

1. Stracci F, Zorzi M, Grazzini G. Colorectal cancer screening: tests, strategies, and perspectives. Front Public Health. 2014; 2: 210.
2. Wolff WI, Shinya H. Polypectomy via the fiberoptic colonoscope: removal of neoplasms beyond reach of the sigmoidoscope. N Engl J Med. 1973; 288: 329-332.
3. Xie YH, Chen YX, Fang JY. Comprehensive review of targeted therapy for colorectal cancer. Signal Transduct Target Ther. 2020; 5(1): 22.
4. Vogelstein B, Fearon ER, Hamilton SR, Kern SE, Preisinger AC, Leppert M, et al. Genetic alterations during colorectal-tumor development. N Engl J Med. 1988; 319(9): 525-532.
5. Czito BG, Willett CG. Thirty years of rectal cancer research: a brief history. Oncology (Williston Park). 2008; 22(12):1441-1442.
6. Brian G. Czito, MD, Christopher G. Willett, MD. Thirty Years of Rectal Cancer Research: A Brief History. Oncology. 2008; 22(12).
7. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993; 328(19):1365-1371.
8. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet. 1996; 348(9040): 1472-1477.
9. Kronborg O, Fenger C, Olsen J, Jørgensen OD, Søndergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet. 1996; 348(9040): 1467-1471.
10. Shaukat A, Mongin SJ, Geisser MS, Lederle FA, Bond JH, Mandel JS, et al. Long-term mortality after screening for colorectal cancer. N Engl J Med. 2013; 369(12): 1106-1114.
11. Peeters KCMJ, Velde CJH, Leer JWH. Marijnen Late Side Effects of Short-Course Preoperative Radiotherapy Combined With Total Mesorectal Excision for Rectal Cancer: Increased Bowel Dysfunction in Irradiated Patients-A Dutch Colorectal Cancer Group Study. Journal of Clinical Oncology. 2005; 23(25): 6199-6206.
12. Höcht S, Hammad R, Thiel H, Wiegel T, Siegmann A, Willner J, et al. A multicenter analysis of 123 patients with recurrent rectal cancer within the pelvis. Front Radiat Ther Oncol. 2004; 38: 41-51.
13. Link KH, Kornmann M, Staib L, Redenbacher M, Kron M, Beger HG, et al. Study Group Oncology of Gastrointestinal Tumors. Increase of survival benefit in advanced resectable colon cancer by extent of adjuvant treatment: results of a randomized trial comparing modulation of 5-FU + levamisole with folinic acid or with interferon-alpha. Ann Surg. 2005; 242(2): 178-187.
14. Giardiello FM, Allen JI, Axilbund JE, Boland CR, Burke CA, Burt RW, et al. US Multi-Society Task Force on Colorectal Cancer. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer. Gastroenterology. 2014; 147(2): 502-526.
15. Fujita K, Kubota Y, Ishida H, Sasaki Y. Irinotecan, a key chemotherapeutic drug for metastatic colorectal cancer. World J Gastroenterol. 2015; 21(43): 12234-12248.
16. Jonker D, Rumble RB, Maroun J. Role of oxaliplatin combined with 5-fluorouracil and folinic acid in the first- and second-line treatment of advanced colorectal cancer. Curr Oncol. 2006; 13(5): 173-184.
17. Taieb J, Gallois C. Adjuvant Chemotherapy for Stage III Colon Cancer. Cancers (Basel). 2020; 12(9): 2679.
18. Garcia J, Hurwitz HI, Alan B. Bevacizumab (Avastin®) in cancer treatment: A review of 15 years of clinical experience and future outlook, Cancer Treatment Reviews. 2020; 86; 102017.
19. Xie YH, Chen YX, Fang JY. Comprehensive review of targeted therapy for colorectal cancer. Sig Transduct Target Ther. 5(1): 2020.
20. Garrett MJ, Waddell JA, Solimando DA. Capecitabine, Oxaliplatin, and Bevacizumab (BCapOx) Regimen for Metastatic Colorectal Cancer. Hosp Pharm. 2017; 52(5): 341-347.
21. Oruç Z, Kaplan MA. Effect of exercise on colorectal cancer prevention and treatment. World J Gastrointest Oncol. 2019; 11(5): 348-366.
22. Knickelbein K, Zhang L. Mutant KRAS as a critical determinant of the therapeutic response of colorectal cancer. Genes Dis. 2015; 2(1): 4-12.
23. Moertel CG, Fleming TR, Macdonald JS, Haller DG, Laurie JA, Goodman PJ, et al. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med. 1990; 322: 352-358.
24. Moertel CG, Fleming TR, Macdonald JS. Levamisole and fluorouracil for adjuvant therapy of resected colon carcinoma. N Engl J Med. 1990; 322: 352-358.
25. Andre T, De Gramont A, Vernerey D, Chibaudel B, Bonnetain F, Tijeras-Raballand A, et al. Adjuvant Fluorouracil, Leucovorin, and Oxaliplatin in Stage II to III Colon Cancer: Updated 10-Year Survival and Outcomes According to BRAF Mutation and Mismatch Repair Status of the MOSAIC Study. J Clin Oncol. 2015; 33(35): 4176-4187.
26. Koncina E, Haan S, Rauh S, Letellier E. Prognostic and Predictive Molecular Biomarkers for Colorectal Cancer: Updates and Challenges. Cancers (Basel). 2020; 12(2): 319.
27. Taieb J, Karoui M, Basile D. How I treat stage II colon cancer patients. ESMO Open. 2021; 6(4): 100184.
28. Soulières D, Greer W, Magliocco AM, Huntsman D, Young S, Tsao

MS, et al. KRAS mutation testing in the treatment of metastatic colorectal cancer with anti-EGFR therapies. Curr Oncol. 2010;17 Suppl 1(Suppl 1): S31-40.

29. Aparicio J, Esposito F, Serrano S, Falco E, Escudero P, Ruiz-Casado A, et al. Metastatic Colorectal Cancer. First Line Therapy for Unresectable Disease. J Clin Med. 2020; 9(12): 3889.
30. Guglielmi AP, Sobrero AF. Second-line therapy for advanced colorectal cancer. Gastrointest Cancer Res. 2007; 1(2): 57-63.
31. Van Cutsem E, Nordlinger B, Cervantes A. ESMO Guidelines Working Group. Advanced colorectal cancer: ESMO Clinical Practice Guidelines for treatment. Ann Oncol. 2010; 21(5): 93-97.
32. Van Cutsem E, Cervantes A, Nordlinger B, Arnold D. ESMO Guidelines Working Group. Metastatic colorectal cancer: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up. Ann Oncol. 2014; 25 Suppl 3: 1-9.
33. Varghese AM, Saltz L. BRAF mutation as a biomarker in colorectal cancer. Advances in Genomics and Genetics. 2015; 7: 347-353.
34. Huyghe N, Baldin P, Van den Eynde M. Immunotherapy with immune checkpoint inhibitors in colorectal cancer: what is the future beyond deficient mismatch-repair tumours? Gastroenterol Rep (Oxf). 2019; 8(1): 11-24.
35. Chae YK, Viveiros P, Lopes G, Sukhadia B, Sheikh MM, Saravia D, et al. Clinical and Immunological Implications of Frameshift Mutations in Lung Cancer. J Thorac Oncol. 2019; 14(10): 1807-1817.
36. Miller A, Asmann Y, Cattaneo L, Braggio E, Keats J, Auclair D, et al. High somatic mutation and neoantigen burden are correlated with decreased progression-free survival in multiple myeloma. Blood Cancer J. 2017; 7(9): e612.
37. Yarchoan M, Johnson BA, Lutz ER, Laheru DA, Jaffee EM. Targeting neoantigens to augment antitumour immunity. Nat Rev Cancer. 2017; 17(4): 209-222.
38. Koulis C, Yap R, Engel R, Jarde T, Wilkins S, Solon G, et al. Personalized Medicine-Current and Emerging Predictive and Prognostic Biomarkers in Colorectal Cancer. Cancers (Basel). 2020; 12(4): 812.