European Review for Medical and Pharmacological Sciences 2021; 25: 480-486

# Association between colorectal cancer and *Streptococcus gallolyticus* subsp. *pasteuranus* (former *S. bovis*) endocarditis: clinical relevance and cues for microbiota science. Case report and review of the literature

A. AGNES[1], A. BIONDI[1], F. BELIA[1], S. DI GIAMBENEDETTO[2], G. ADDOLORATO[1], M. ANTONELLI[1], D. D'UGO[1], R. PERSIANI[1]

[1]Department of Medical and Surgical Studies, Fondazione Policlinico Universitario A. Gemelli IRCSS, Università Cattolica del Sacro Cuore, Rome, Italy
[2]Department of Laboratory and Infectious Disease Monitoring Studies, Fondazione Policlinico Universitario A. Gemelli IRCSS, Università Cattolica del Sacro Cuore, Rome, Italy

**Abstract. – OBJECTIVE: The purpose of this paper is to contextualize the case of a patient with a synchronous diagnosis of colorectal cancer (CRC) and endocarditis from *S. gallolyticus* subsp. *pasteuranus* (former *S. Bovis*) within the current evidence, in order to determine if this condition is indicative of an underlying CRC and if it has any pathophysiologic significance.**

**PATIENTS AND METHODS: First, we describe the clinical case. Then, we review the literature focused on the association between infections from the former *S. Bovis* group and CRC and on the possible role of certain microbiota species on the occurrence of CRC. At last, we discuss the implications of this case considering the current evidence.**

**RESULTS: There is a strong association between all the species of the former *S. Bovis* group and CRC. There is initial evidence that these bacteria may contribute to CRC by a genomic *passenger* mechanism.**

**CONCLUSIONS: There are two main conclusions for this paper. The first one is that CRC neoplasms and endocarditis from all species of the former *S. bovis* group have a strong association. Any case of infection by these subspecies should prompt to a diagnostic completion by colonoscopy. The second one is that there is an increased need for detailed reports/series and original articles based on the evaluation of gut microbiota in patients with CRC, with the aim to clarify if the association between bacteria and CRC is causative or sporadic and to better understand the possible causative mechanism of specific bacteria in initiating and promoting CRC.**

*Key Words:*
Colorectal cancer, Microbiota, Colorectal surgery, Complications.

## Introduction

In 2018, 1,849,518 new cases of colorectal cancer (CRC) were diagnosed globally. CRC represents the third most common cancer worldwide and the 10.2% of all new cases of cancer. It is the second leading cause of cancer death in men and the third leading cause in women. As many other neoplasms, due to the relative paucity of symptoms, it is difficult to diagnose it timely in patients that choose not to undergo a regular screening. Patients in stage IV at diagnosis are at least 20%[1]. Hence, the importance of a timely diagnosis is essential to treat this disease while still in a curative stage.

In previous years, a significant and unambiguous association between endocarditis caused by *Streptococcus Bovis* and colorectal adenoma and carcinoma was described. After change in the taxonomy of the *S. bovis* group[2], many reports have described a selective association between a specific subspecies (*S. gallolyticus* subsp. *gallolyticus*) and CRC[3,4]. However, there are controversies in this field, as this association has been described even for other subtypes, as *S. gallolyticus* subsp. *pasteuranus*.

In recent years, the study of gut microbiota has been under the spotlight. Nowadays, it appears clear that its balance is necessary for intestinal health maintenance. More and more associations between specific bacteria and gut function are emerging[5]. A specific chapter of microbiota science is dedicated to the determination of its pos-



*Corresponding Author:* Alberto Biondi, MD; e-mail: biondi.alberto@gmail.com

sible initiating role for CRC. The former *S. bovis* group has been involved in this investigation due to various reports of its detection in CRC cancer tissue and to the strong clinical association between endocarditis or infection from this bacteria and CRC[6-8].

In this report, we describe the case of a 62-year-old male with a synchronous diagnosis of *Streptococcus gallolyticus* subsp. *pasteuranus* endocarditis and of asymptomatic colorectal cancer. We review the pertinent literature, stressing the importance of this association from a clinical point of view. At last, we collocate this report in the debate on the role of microbiota in the development of CRC.

## Case Report

A sixty-two-year-old male in good general conditions presented to surgical attention in an outpatient clinic in February 2020. The patient had undergone a colonoscopy nine days before, after a positive fecal occult blood test, which he underwent for screening. The colonoscopy showed a circumferential thickening of the mucosa and the colic wall located in the median third of the ascending colon (Figure 1). The pathologic results of the endoscopic biopsy documented the presence of adenocarcinoma. He had hypertension and no history of cardiac valve disease. At the clinical evaluation, he had a good performance status. However, he complained of a remitting fever and asthenia since December 2019. The fever had maximum peaks of 38.5°C but was under 38°C for most of the time, mostly occurring in the evening and night hours, associated to nocturnal sweating. He had multiple courses of antibiotic therapy with no benefit, except for a 10-day course of Levofloxacin in January, that resulted in a temporary remission of the symptomatology. An infective disease evaluation was immediately planned. After evaluation, the patient underwent blood, sputum and fecal cultures and a transthoracic echocardiogram that showed a small vegetation on the anterior flap of the mitral valve associated with minimal mitral insufficiency and moderate aortic insufficiency. The CRP was 63.7 mg/dl, the hemoglobin 9.8 g/dl. After one day, the blood cultures tested positive for *Streptococcus spp.* and he was admitted to the infective disease ward. He started antibiotic therapy with Ceftriaxone. A transesophageal echocardiogram confirmed the presence of a small floating vegetation attached to the anterior flap of the mitral valve (9×4 mm). Moreover, it documented a suspect small vegetation of the aortic valve (5×4) (Figure 2). For this reason, the patient also underwent an encephalic MRI that documented no clear sign of embolism or ischemia. No neurological symptoms were present. The results of the blood cultures documented positivity for a *Streptococcus*

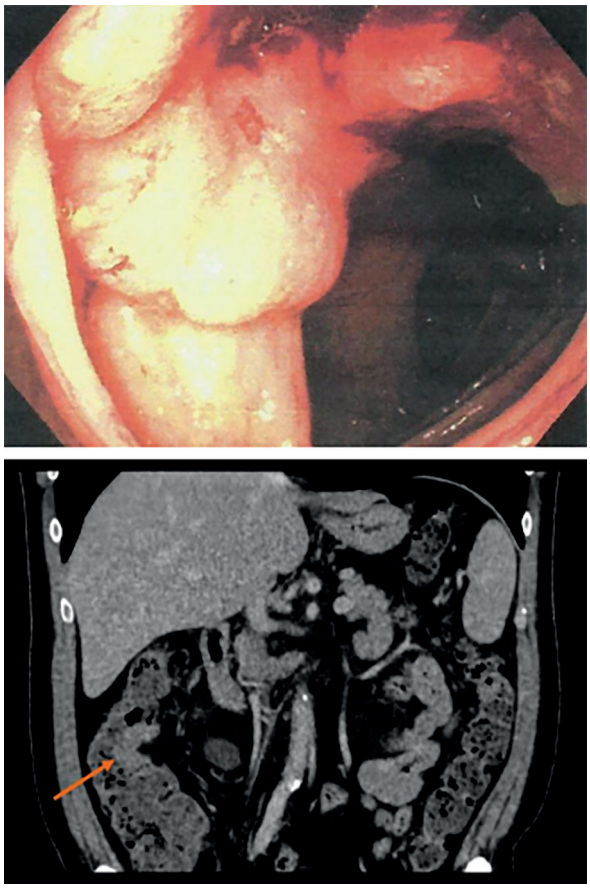

**Figure 1.** Images of the neoplasm at colonoscopy and CT.

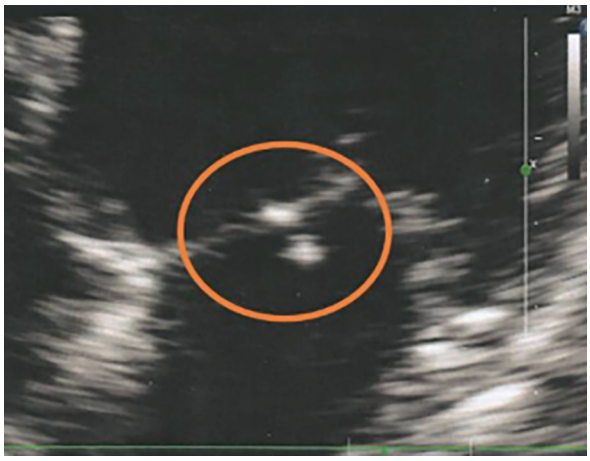

**Figure 2.** Echocardiographic image of the vegetation.

*gallolyticus* subsp. *pasteuranus (spectrometric identification)* sensible to Ceftriaxone. During the stay, the fever completely subsided. To complete the staging, a thoraco-abdominal contrast CT scan was planned. The CT scan (data) documented a cT2-3NxM0 neoplasm of the ascending colon (Figure 1). After 10 days from admission, he repeated an echocardiogram that did not document any cardiac valve vegetation. After thirteen days from admission, the blood cultures tested negative. The CRP was 5.7 mg/dl. After fourteen days from admission, he was discharged in good clinical conditions. He underwent therapy with Ceftriaxone for further 15 days and an echocardiographic control that resulted negative for cardiac valve vegetation. After 20 days from the end of therapy and 55 days from the diagnosis, he was admitted to the surgical ward. An Enhanced Recovery After Surgery (ERAS) protocol was applied for the perioperative management and synbiotics were administered in the perioperative period as well. A laparoscopic right hemicolectomy was performed. Cultural exams of the tumor mucosa and the intraluminal feces were ordered. The postoperative stay was uneventful, and the patient was discharged on postoperative day 3. No 30-days complications were detected. The pathologic results on the specimen documented a poorly differentiated pT3N0 colic adenocarcinoma MLH1+, PPMS2+, MSH2+, MSH6+, and CDX2+. The cultural exam executed on the tumor mucosa and the one conducted on the luminal content feces nearby the tumor were comparable, documenting the presence of Enterobacter spp., *Enterococcus spp. (faecalis and faecium)*, *Citrobacter Freundii*, *Bacteroides spp (fragilis and ovatus)*, and *Clostridium innocuum*.

## Discussion and Review of the Literature

In this report, we describe the case of a 62-year-old male with a synchronous diagnosis of *Streptococcus gallolyticus* subsp. *pasteuranus* (former *S. Bovis*) endocarditis and asymptomatic colorectal cancer.

*S. bovis* is a gram-positive group D streptococcus. The association between *S. bovis* endocarditis and CRC has been extensively described. Indeed, in 1974, Hoppes et al[9] described the presence of colonic adenomas or carcinomas in 64% of patients with *S. Bovis* endocarditis and since then, many other reports have confirmed this association[8-11]. In 2003, a new taxonomic system for group D streptococci and for the former *S. Bovis* species has been defined, based on the detection of the ability of the bacteria to ferment mannitol, on bile-esculin reaction, acidification of trehalose, hydrolysis of starch and on sequence-based genomic analysis. The new classification includes four subspecies instead of the *S. bovis* group, namely, *Streptococcus gallolyticus* subsp. *gallolyticus* (biotype I), *Streptococcus infantarius* subsp. *infantarius* and *Streptococcus infantarius* subsp. *coli* (biotype II/1) and *Streptococcus gallolyticus* subsp. *pasteuranus* (biotype II/2)[2]. After the subspecies identification, most of the reports on the association between CRCs and endocarditis have focused on *Streptococcus gallolyticus* subsp. *gallolyticus*. Indeed, this subspecies presents the strongest association with CRC. In 1989, Ruoff et al[11] identified an association between bacteremia from *Streptococcus gallolyticus* subsp. *gallolyticus* and CRC (71% of patients). In 2005, Corredoira et al[12] confirmed a similar pattern of association, identifying an association between positive cultures for *Streptococcus gallolyticus* subsp. *gallolyticus* and CRC in 57% of cases (24 of 42 patients). These results were confirmed in a 2011 systematic review and meta-analysis, reporting an association between infection from *Streptococcus gallolyticus* subsp. *gallolyticus* and CRC in 65% of cases. The risk of CRC in patients with *Streptococcus gallolyticus* subsp. *gallolyticus* was significantly increased (odds ratio 7.26, CI 95% 3.94-13.36)[13]. In some papers, a clinically relevant association for *Streptococcus gallolyticus* subsp. *pasteuranus* and meningitis but no association with CRC was described[3,14]. Other authors reported their data on the incidence of colorectal adenomas in patients with *Streptococcus gallolyticus* subsp. *pasteuranus* as comparable to the one described in studies of screening in the general population[15]. Instead, in another paper, a 31% association with colorectal neoplasms was detected for *Streptococcus gallolyticus* subsp. *pasteuranus* bacteremia[8]. For this reason, some authors concluded that all endocarditis from the former *S. Bovis* should be investigated with colonoscopy[8,16]. In this regard, it should be noted there is controversy on the methods used to identify subspecies of the former *S. Bovis* group, as most still rely on biochemical/phenotypical-based assays, which have showed some inconsistency. Instead, spectrometric and sequencing-based techniques have been addressed as more reliable. Although they are not widely available and associated with increased costs[3].

Streptococci have a well-known tropism for native valves, as endocarditis caused by the *Streptococcus* spp. is one of the most frequent causes of endocarditis[17]. *S. gallolyticus* subps. *gallolyticus* endocarditis has been reported in 94% of patients with bacteremia and in the 74% of patients with *S. gallolyticus* subsp. *gallolyticus* isolates[11,12]. Infective endocarditis from *S. Bovis* usually affects the left cardiac valves. Vegetations are often small, and TEE is recommended as TTE may be non-diagnostic[8]. The mechanism of hematogenous diffusion of this bacterium is still unclear. It has been suggested that colonic lesions may provide a specific niche for S. bovis/gallolyticus. The result is a tumor-associated silent infection that may enter blood circulation after the occurrence of tumor micro perforations[4,18]. Notably, the condition of asymptomatic *S. bovis* carrier has been identified, while the majority of endocarditis from *S.Bovis* has been reported in patients with an immunosuppressive condition or a cardiac valve disease[4,8]. Moreover, a simultaneous occurrence of chronic liver disease and colon cancer in patients with S. bovis/gallolyticus endocarditis/bacteremia has been reported in 3-57% of cases. This has been hypothesized to be linked to an increased rate of bypass of the hepatic reticulo-endothelial system thanks to the portal hypertension, favoring the access to systemic circulation[8,18,19]. In our case, the patient was in good general conditions, with minimal-mild valve insufficiency, no history of liver disease, and he had a locally advanced CRC with no ulceration or local ascessualization.

The etiologic mechanism beyond the origin of CRC is multifactorial and has yet to be fully understood. Dysbiosis has been strongly related to inflammatory bowel diseases (IBDs), which are a well-known high-risk condition for CRC[20]. Even the genomic changes initiating non-IBD associated CRC have been postulated to occur in an "inflammatory" microenvironment[21]. Recently, a molecular classification for CRC has been proposed, including four subtypes (CSM 1-4), one of which (the mesenchymal subtype) has been associated with an angiogenic, inflammatory, and immunosuppressive signature[22,23]. From a genetic/epigenetic point of view, the mutations leading to CRC development have been classically distinguished in two categories. The "driver mutations", that give to the mutated cells an effective advantage in the neoplastic transformation, and the "passenger" mutations, that do not have a direct effect on tumor progression. Most CRCs have been identified to originate from an adenoma-carcinoma sequence. It consists of "driver" mutations affecting the *APC-kRAS-p53* pathway. In recent years, the association between gut bacteria and certain diseases have been contextualized in the broader chapter of the gut microbiota science. The gut microbiota is defined as the totality of the microorganisms that reside in the gastrointestinal tract. It has been furtherly divided in a mucosal associated microbiota (MAM) and a luminal microbiota (LM)[24]. Tjalsma et al[21], in 2012, theorized an association between gut microbiota and cancer according to a *driver-passenger* model. According to this model, *driver* bacteria that colonize colonic mucosa, such as *Enterococcus faecalis*, *Escherichia coli* or *Bacteroides Fragilis*, could initiate CRC development causing persistent inflammation, cell proliferation and genotoxicity. While promoting carcinogenesis, *driver*-bacteria also have an indirect role on tumor progression. They could create the appropriate environment for the development of *passenger*-bacteria: secondary colonizers that could suppress carcinogenesis (i.e., probiotic passenger bacteria) or promote it (pathogenic passenger bacteria). In this regard, increased levels of *Fusobacterium* have been related with CRC stage, age of incidence and tumor location[25]. The strong association between infection from *S. Bovis* and colonic adenomas and carcinomas have led to the speculation on the possible oncogenic (*driver* or *passenger*) role of this bacterium. Indeed, in 1977, Klein et al[26] reported the presence of *S. bovis* in the fecal cultures of 35 of 63 (56%) investigated patients with CRC. This report was confirmed in further studies[27,28] even though others did not confirm this association[29,30]. In 2018, Rezasoltani et al[6] documented the presence of *S. Bovis* in colorectal adenomas, especially tubular, villous and tubulovillous ones, while this presence was not documented in serrated polyps. Abdulamir et al[31], as well, identified a significantly increased rate of detectable *S. gallolyticus* DNA in CRC tissues compared with healthy colonic tissues (49 *vs.* 8%). In light of these reports, it has been postulated that the presence of *S. bovis*, and in particular *S. gallolyticus subsp gallolyticus,* may have a role in driving adenomas into an advanced stage through the promotion of proinflammatory pathways[4]. Moreover, genomic *passenger* mechanisms, intended as the advantage in adhering to CRC cells promoting their proliferation, have

actually been identified in specific strains of *S. gallolyticus* subsp. *gallolyticus*[32]. However, in 2019, a Danish study[17] investigated the presence of any correlation between colorectal adenomas, CRC and the presence of *S. gallolyticus* or *Streptococcus gallolyticus* subsp. *gallolyticus* in the paraffin-embedded tissues of 195 patients. Their quantitative PCR + 16s ribosomal RNA gene sequencing did not document its presence in any of the investigated samples. The difficulty in extracting DNA from gram-positive bacteria as *S. gallolyticus* and patients' geographic location were discussed as a possible limitation of this study due to its discordant results compared with the previous ones. In our study, the tissue and fecal cultures did not identify the presence of *S. gallolyiticus* neither in the MAM nor in the LM. It is unclear if the perioperative application of the ERAS protocol and of the administration of synbiotics may have contributed to this finding.

In our case, the late diagnosis of endocarditis did not cause a worsening in patient's status nor a delay in diagnosis. The only significant delay due to the need for treatment of the endocarditis was the one between diagnosis and treatment (55 days). However, cases of *S. Bovis* endocarditis treated and cured 6 years before the presentation of a IV stage colonic cancer have also been described, underlining a possibly problematic poor knowledge of this association between clinicians[33].

## Conclusions

There are two main conclusions for this report and review of the literature. The first and most important one is the emerging need for all clinicians to be aware of the strong association between CRC neoplasms and endocarditis from the former *S. bovis* group, including *S. gallolyticus* subsp. *gallolyticus* and, more rarely, *S. gallolyticus* subsp. *pasteuranus* and other subtypes. From an epidemiologic point of view, reporting the subspecies remains very important. However, from a clinical point of view, the detection of any case of infection by these subspecies should prompt to a diagnostic completion by colonoscopy to search for asymptomatic colonic adenomas or CRC. The second conclusion is a consideration for gut microbiota-based translational research. In the literature, there is not enough evidence to determine if the association between bacteria and CRC is causative or sporadic. There is an increased need for detailed reports/series and original articles based on the evaluation of gut microbiota in patients with CRC, in order to increase the comprehension on this topic. In the future, if this field of research is adequately developed, many advantages are expected for the management of CRC from a preventive, diagnostic and therapeutic point of view.

### Conflict of Interest

The Authors declare that they have no conflict of interests.

### Consent to Participate (include appropriate statements)

The patient expressed its consent to participation in this study.

### Consent for Publication (include appropriate statements)

The patient expressed its consent to the publication of this study.

### Availability of Data and Material (data transparency)

Available by request.

## References

1) Global Cancer Observatory GLOBOCAN Online Database - 2018. http://gco.iarc.fr/. Accessed 11 Dec 2019.
2) Schlegel L, Grimont F, Ageron E, Grimont PAD, Bouvet A. Reappraisal of the taxonomy of the Streptococcus bovis/Streptococcus equinus complex and related species: description of Streptococcus gallolyticus subsp. gallolyticus subsp. nov., S. gallolyticus subsp. macedonicus subsp. nov. and S. gallolyticus subsp. pasteurianus subsp. nov. Int J Syst Evol Microbiol 2003; 53: 631-645.
3) Dekker JP, Lau AF. An Update on the Streptococcus bovis Group: Classification, Identification, and Disease Associations. J Clin Microbiol 2016; 54: 1694-1699.
4) Boleij A, Tjalsma H. The itinerary of Streptococcus gallolyticus infection in patients with colonic malignant disease. Lancet Infect Dis 2013; 13: 719-724.
5) Macchione IG, Lopetuso LR, Ianiro G, Napoli M, Gibiino G, Rizzatti G, Petito V, Gasbarrini A, Scaldaferri F. Akkermansia muciniphila: key player in metabolic and gastrointestinal disorders. Eur Rev Med Pharmacol Sci 2019; 23: 8075-8083.

6) Rezasoltani S, Asadzadeh Aghdaei H, Dabiri H, Akhavan Sepahi A, Modarressi MH, Nazemalhosseini Mojarad E. The association between fecal microbiota and different types of colorectal polyp as precursors of colorectal cancer. Microb Pathog 2018; 124: 244-249.

7) Bundgaard-Nielsen C, Baandrup UT, Nielsen LP, Sørensen S. The presence of bacteria varies between colorectal adenocarcinomas, precursor lesions and non-malignant tissue. BMC Cancer 2019; 29; 19: 399.

8) Lazarovitch T, Shango M, Levine M, Brusovansky R, Akins R, Hayakawa K, Lephart PR, Sobel JD, Kaye KS, Marchaim D. The relationship between the new taxonomy of Streptococcus bovis and its clonality to colon cancer, endocarditis, and biliary disease. Infection 2013; 41: 329-337.

9) Hoppes WL, Lerner PI. Nonenterococcal group-D streptococcal endocarditis caused by Streptococcus bovis. Ann Intern Med 1974; 81: 588-593.

10) Olmos C, Vilacosta I, Sarriá C, López J, Ferrera C, Sáez C, Vivas D, Hernández M, Sánchez-Enrique C, García-Granja PE, Pérez-Cecilia E, Maroto L, San Román JA. Streptococcus bovis endocarditis: update from a multicenter registry. Am Heart J 2016; 171: 7-13.

11) Ruoff KL, Miller SI, Garner CV, Ferraro MJ, Calderwood SB. Bacteremia with Streptococcus bovis and Streptococcus salivarius: clinical correlates of more accurate identification of isolates. J Clin Microbiol 1989; 27: 305-308.

12) Corredoira JC, Alonso MP, García JF, Casariego E, Coira A, Rodriguez A, Pita J, Louzao C, Pombo B, López MJ, Varela J. Clinical characteristics and significance of Streptococcus salivarius bacteremia and Streptococcus bovis bacteremia: a prospective 16-year study. Eur J Clin Microbiol Infect Dis 2005; 24: 250-255.

13) Boleij A, van Gelder MM, Swinkels DW, Tjalsma H. Clinical Importance of Streptococcus gallolyticus infection among colorectal cancer patients: systematic review and meta-analysis. Clin Infect Dis 2011; 53: 870-878.

14) Cohen LF, Dunbar SA, Sirbasku DM, Clarridge JE 3rd. Streptococcus bovis infection of the central nervous system: report of two cases and review. Clin Infect Dis 1997; 25: 819-823.

15) Sánchez JC, García-Garrote F, Coira A, López-Agreda H, Alonso-García MP. Colorectal neoplasia associated with Streptococcus gallolyticus subspecies pasteurianus. Lancet Infect Dis 2014; 14: 272-273.

16) Takamura N, Kenzaka T, Minami K, Matsumura M. Infective endocarditis caused by Streptococcus gallolyticus subspecies pasteurianus and colon cancer. BMJ Case Rep 2014; 2014: bcr2013203476.

17) Murdoch DR, Corey GR, Hoen B, Miró JM, Fowler VG Jr, Bayer AS, Karchmer AW, Olaison L, Pappas PA, Moreillon P, Chambers ST, Chu VH, Falcó V, Holland DJ, Jones P, Klein JL, Raymond NJ, Read KM, Tripodi MF, Utili R, Wang A, Woods CW, Cabell CH; International Collaboration on Endocarditis-Prospective Cohort Study (ICE-PCS) Investigators. Clinical presentation, etiology, and outcome of infective endocarditis in the 21st century: the International Collaboration on Endocarditis-Prospective Cohort Study. Arch Intern Med 2009; 169: 463-473.

18) Gupta A, Madani R, Mukhtar H. Streptococcus bovis endocarditis, a silent sign for colonic tumour. Colorectal Dis 2010; 12: 164-171.

19) Abdulamir AS, Hafidh RR, Abu Bakar F. The association of Streptococcus bovis/gallolyticus with colorectal tumors: the nature and the underlying mechanisms of its etiological role. J Exp Clin Cancer Res 2011; 30: 11.

20) Keller DS, Windsor A, Cohen R, Chand M. Colorectal cancer in inflammatory bowel disease: review of the evidence. Tech Coloproctol 2019; 23: 3-13.

21) Tjalsma H, Boleij A, Marchesi JR, Dutilh BE. A bacterial driver-passenger model for colorectal cancer: beyond the usual suspects. Nat Rev Microbiol 2012; 10: 575-582.

22) Guinney J, Dienstmann R, Wang X, de Reyniès A, Schlicker A, Soneson C, Marisa L, Roepman P, Nyamundanda G, Angelino P, Bot BM, Morris JS, Simon IM, Gerster S, Fessler E, De Sousa E Melo F, Missiaglia E, Ramay H, Barras D, Homicsko K, Maru D, Manyam GC, Broom B, Boige V, Perez-Villamil B, Laderas T, Salazar R, Gray JW, Hanahan D, Tabernero J, Bernards R, Friend SH, Laurent-Puig P, Medema JP, Sadanandam A, Wessels L, Delorenzi M, Kopetz S, Vermeulen L, Tejpar S. The consensus molecular subtypes of colorectal cancer. Nat Med. 2015; 21: 1350-1356.

23) Fessler E, Medema JP. Colorectal cancer subtypes: developmental origin and microenvironmental regulation. Trends Cancer 2016; 2: 505-518.

24) Van den Abbeele P, Van de Wiele T, Verstraete W, Possemiers S. The host selects mucosal and luminal associations of coevolved gut microorganisms: a novel concept. FEMS Microbiol Rev 2011; 35: 681-704.

25) Viljoen KS, Dakshinamurthy A, Goldberg P, Blackburn JM. Quantitative profiling of colorectal cancer-associated bacteria reveals associations between fusobacterium spp., enterotoxigenic Bacteroides fragilis (ETBF) and clinicopathological features of colorectal cancer. PLoS One 2015; 10: e0119462.

26) Klein RS, Recco RA, Catalano MT, Edberg SC, Casey JI, Steigbigel NH. Association of Streptococcus bovis with carcinoma of the colon. N Engl J Med 1977; 297: 800-802.

27) Al-Jashamy K, Murad A, Zeehaida M, Rohaini M, Hasnan J. Prevalence of colorectal cancer associated with Streptococcus bovis among inflammatory bowel and chronic gastrointestinal tract dis-

ease patients. Asian Pac J Cancer Prev 2010; 11: 1765-1768.

28) Shanan S, Gumaa SA, Sandström G, Abd H. Significant association of Streptococcus bovis with malignant gastrointestinal diseases. Int J Microbiol 2011; 2011: 792019.

29) Dubrow R, Edberg S, Wikfors E, Callan D, Troncale F, Vender R, Brand M, Yapp R. Fecal carriage of Streptococcus bovis and colorectal adenomas. Gastroenterology 1991; 101: 721-725.

30) Potter MA, Cunliffe NA, Smith M, Miles RS, Flapan AD, Dunlop MG. A prospective controlled study of the association of Streptococcus bovis with colorectal carcinoma. J Clin Pathol 1998; 51: 473-474.

31) Abdulamir AS, Hafidh RR, Bakar FA. Molecular detection, quantification, and isolation of Streptococcus gallolyticus bacteria colonizing colorectal tumors: inflammation-driven potential of carcinogenesis via IL-1, COX-2, and IL-8. Mol Cancer 2010; 9: 249.

32) Kumar R, Herold JL, Taylor J, Xu J, Xu Y. Variations among Streptococcus gallolyticus subsp. gallolyticus strains in connection with colorectal cancer. Sci Rep 2018; 8: 1514.

33) Ferrari A, Botrugno I, Bombelli E, Dominioni T, Cavazzi E, Dionigi P. Colonoscopy is mandatory after Streptococcus bovis endocarditis: a lesson still not learned. Case report. World J Surg Onc