J Gastric Cancer. 2024 Jan;24(1):89-98
https://doi.org/10.5230/jgc.2024.24.e4
pISSN 2093-582X·eISSN 2093-5641

Journal of Gastric Cancer

Review Article

Unveiling the Gastrointestinal Microbiome Symphony: Insights Into Post-Gastric Cancer Treatment Microbial Patterns and Potential Therapeutic Avenues

Chan Hyuk Park

Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, Guri, Korea

Received: Nov 12, 2023
Revised: Dec 1, 2023
Accepted: Dec 4, 2023
Published online: Dec 22, 2023

Correspondence to
Chan Hyuk Park
Department of Internal Medicine, Hanyang University Guri Hospital, Hanyang University College of Medicine, 153 Gyeongchun-ro, Guri 11923, Korea.
Email: yesable7@gmail.com

ORCID iDs
Chan Hyuk Park
https://orcid.org/0000-0003-3824-3481

Funding
This work was supported by the National Research Foundation of Korea (NRF) grant funded by the Korean Government (MSIT) (No. NRF-2021R1C1C1005728) (C.H.P.). Figs. 1 and 2 were created using Biorender.

Conflict of Interest
No potential conflict of interest relevant to this article was reported.

ABSTRACT

This review delved into the intricate relationship between the gastrointestinal microbiome and gastric cancer, particularly focusing on post-treatment alterations, notably following gastrectomy, and the effects of anticancer therapies. Following gastrectomy, analysis of fecal samples revealed an increased presence of oral cavity aerotolerant and bile acid-transforming bacteria in the intestine. Similar changes were observed in the gastric microbiome, highlighting significant alterations in taxon abundance and emphasizing the reciprocal interaction between the oral and gastric microbiomes. In contrast, the impact of chemotherapy and immunotherapy on the gut microbiome was subtle, although discernible differences were noted between treatment responders and non-responders. Certain bacterial taxa showed promise as potential prognostic markers. Notably, probiotics emerged as a promising approach for postgastrectomy recovery, displaying the capacity to alleviate inflammation, bolster immune responses, and maintain a healthy gut microbiome. Several strains, including *Bifidobacterium*, *Lactobacillus*, and *Clostridium butyricum*, exhibited favorable outcomes in postoperative patients, suggesting their potential roles in comprehensive patient care. In conclusion, understanding the intricate interplay between the gastrointestinal microbiome and gastric cancer treatment offers prospects for predicting responses and enhancing postoperative recovery. Probiotics, with their positive impact on inflammation and immunity, have emerged as potential adjuncts in patient care. Continued research is imperative to fully harness the potential of microbiome-based interventions in the management of gastric cancer.

Keywords: Gastric cancer; Microbiome; Gastrectomy; Chemotherapy; Immunotherapy

INTRODUCTION

The human gastrointestinal tract hosts an extensive microbial population of up to 10^{14} microorganisms, playing diverse roles in immune system development, pathogen defense, carbohydrate breakdown, and detoxification [1,2]. The advent of advanced sequencing techniques like 16S rRNA gene sequencing and whole-genome sequencing has revolutionized

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microbial investigation [3]. These techniques facilitate the identification of previously uncultured bacteria, allowing for the examination of microbial variations across different disease conditions [4-7].

Recent scientific interest has surged in exploring the correlation between gastric cancer and the gastrointestinal microbiome [8]. While *Helicobacter pylori* has long been recognized as the most strongly associated microorganism with gastric cancer, recent studies have unveiled numerous other microbes linked to this condition [8]. Moreover, changes in the gastric microbiome have bee connected with alterations in the overall microbial community within the intestine, often associated with conditions such as colorectal cancer [9,10]. Additionally, there is a growing focus on studying changes in the gastrointestinal microbiome following gastric cancer treatment, particularly post-gastrectomy [11]. Understanding these post-treatment changes is pivotal for predicting prognosis and identifying potential therapeutic targets to prevent recurrence. This review aims to explore the alterations in the oral, gastric, and intestinal microbiomes subsequent to gastric cancer treatment and their clinical implications.

UNDERSTANDING ALPHA AND BETA DIVERSITY METRICS IN MICROBIOME RESEARCH

Before discussing this comprehensive review, I will briefly explore the commonly used diversity metrics in microbiome research. This will assist readers unfamiliar with microbiome studies in understanding this article. In microbiome research, alpha-diversity refers to the diversity of species within a single sample or community [12]. It assesses species richness (the number of different species) and evenness (how evenly the species are distributed) within a particular sample. Common metrics used to calculate alpha diversity include the Chao1 index, which estimates species richness, and the Shannon index, which considers both richness and evenness [13,14]. On the other hand, beta-diversity focuses on the differences in species composition between different samples or communities [15]. It evaluates the degree of similarity or dissimilarity in species diversity among samples. Several methods are used to measure beta diversity, such as Bray-Curtis dissimilarity or UniFrac distances, which quantify the differences in species present between samples [16,17]. These diversity indices and metrics are essential tools for understanding and comparing the diversity of microbial communities and aid researchers in uncovering patterns, ecological relationships, and changes within complex systems.

GUT MICROBIOME AFTER GASTRECTOMY

The gut microbiome, primarily analyzed using fecal samples, is the focal point of current gastrointestinal microbial research [10]. Fecal samples are more readily accessible compared to mucosal samples, making them the preferred choice for gut microbiome analysis. Additionally, due to the potential clinical relevance of the gut microbiome as a biomarker, the microbial content in fecal samples holds higher clinical significance than that in mucosal samples. Research exploring changes in the gut microbiome post-gastric cancer surgery has largely centered on fecal samples, offering valuable insights into this area.

Understanding the dynamics of microbiome alterations following gastric cancer surgery necessitates comprehension of the physiological changes subsequent to gastrectomy (**Fig. 1**).

https://doi.org/10.5230/jgc.2024.24.e4

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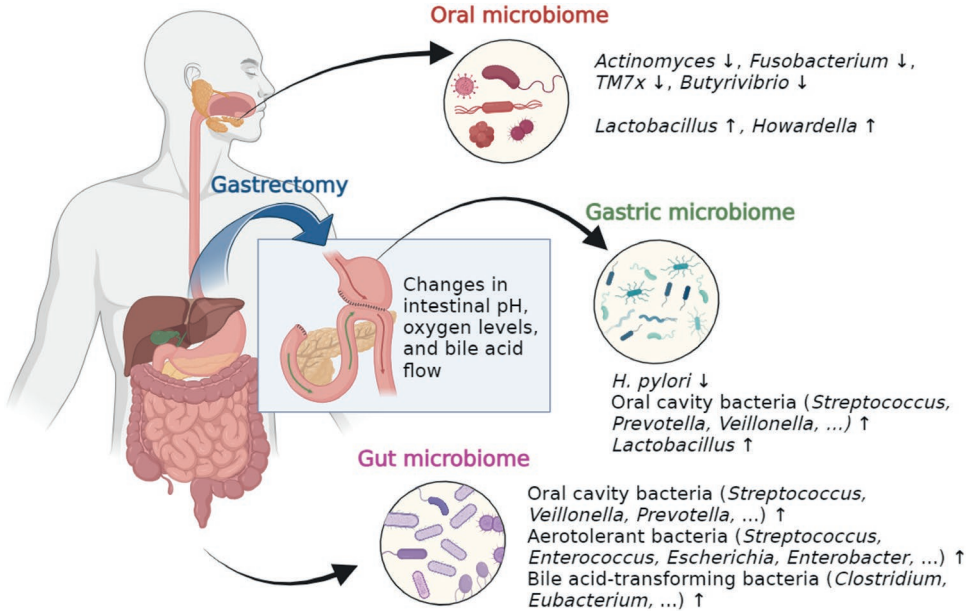

Fig. 1. Changes in the microbiome composition of the digestive tract after gastric cancer surgery. Gastrectomy in patients with gastric cancer induces alterations in the composition of the gastrointestinal microbiome due to changes in intestinal pH, oxygen levels, and bile acid flow. In the stomach, these changes result in a decrease in the relative abundance of *H. pylori*, whereas the bacteria commonly observed in the oral cavity are more prevalent in the stomach. Similar changes were observed in the gut, with an increased relative abundance of oral cavity, aerotolerant, and bile acid-transforming bacteria after gastrectomy. These alterations suggest that oral bacteria predominantly flow from the mouth to the intestines through the stomach, becoming more apparent after a certain period post-surgery and persisting over an extended period. Interestingly, the changes in microbiome composition following gastric cancer surgery are not limited to the stomach and gut, but are also observed in the oral cavity. Post-surgery, the relative abundance of *Lactobacillus* increased, while *Fusobacterium*, *TM7x*, and *Butyrivibrio* decreased compared to pre-surgery levels. These observations are consistent with the findings of the gastric microbiome after gastrectomy. The increase in gastric or bile acid reflux after gastrectomy, coupled with factors such as weight loss, hormonal changes, and metabolomic changes, suggests that the oral microbiome is influenced by gastrectomy.

Gastric barrier loss due to gastrectomy triggers variations in intestinal pH, oxygen levels, and bile acid flow. These changes result in an increased presence of oral cavity, aerotolerant, and bile acid-transforming bacteria in the intestine. Erawijantari et al. [18] conducted a comprehensive investigation of the postgastrectomy gut microbiome using whole-genome sequencing. Fecal samples were collected from 50 patients who underwent gastrectomy for gastric cancer and 56 individuals without prior gastrointestinal surgery. Among the patients, 12 underwent total gastrectomy, while 38 underwent subtotal gastrectomy. The relative frequencies of aerobes (*Streptococcus* and *Enterococcus*) and facultative anaerobes (*Escherichia*, *Enterobacter*, and *Streptococcus*) were significantly higher in the gastrectomy group compared to the control group, attributed to increased intestinal oxygen levels post-gastrectomy [19]. Moreover, common oral cavity microorganisms like *Streptococcus*, *Veillonella*, and *Prevotella* [20] were abundant in the gut microbiome of gastrectomy patients. This suggests a migration of oral microbes into the intestine due to elevated intestinal pH and loss of the normal gastric barrier function [21,22]. Metabolome analysis alongside microbiome analysis by Erawijantari et al. [18] revealed an enrichment of the secondary bile acid, deoxycholic acid, in the gastrectomy group. This enrichment is believed to be a consequence of altered bile flow post-gastrectomy, stimulating the growth of bile acid-transforming bacteria. While not statistically significant, there was an observable trend towards a higher abundance of *Clostridium* and *Eubacterium* in the gastrectomy group compared to the control group [18]. Overall, gut microbial diversity and richness were higher in the gastrectomy group compared to the control group [18].

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The variation in gut microbial composition between patients who underwent gastrectomy and healthy individuals was confirmed by Lin et al. [23]. The analysis involved fecal samples from 28 patients who had partial gastrectomy for gastric cancer (14 with Billroth II anastomosis and 14 with Roux-en-Y gastrojejunostomy) and 14 healthy individuals in the control group. Both the Chao1 index, an estimator of bacterial richness, and the Shannon index, encompassing richness and evenness, were higher in the gastrectomy group, implying a greater diversity in the gut microbial composition of these patients. At the genus level, the analysis revealed a higher relative abundance of various genera including *Oscillospira*, *Prevotella*, *Coprococcus*, *Veillonella*, *Clostridium*, *Desulfovibrio*, *Anaerosinus*, *Slackia*, *Oxalobacter*, *Victivallis*, *Butyrivibrio*, *Sporobacter*, and *Campylobacter* in the gastrectomy group compared to the control group [23]. As the study included patients who had undergone gastrectomy approximately 8 years prior, it suggests that differences in gut microbial composition may persist in the long term.

Horvath et al. [24] analyzed the fecal microbiome of 14 patients who underwent upper partial gastrectomy and Billroth II anastomosis and compared them with eight in-house relatives as a control group. The gastrectomy group exhibited a higher abundance of typical oral bacteria (*Veillonella*, *Oribacterium*, and *Mogibacterium*) along with *Escherichia–Shigella*, *Enterococcus*, and *Streptococcus*. This aligns with other research findings, suggesting that changes in the oral microbiome due to anatomical and physiological alterations following gastrectomy may impact the composition of the gut microbiome. However, in contrast to similar studies [18,23], the Shannon index in the gastrectomy group was lower than that in the control group. This discrepancy might have been influenced by the relatively small sample size, warranting further investigation.

The studies mentioned above compared gastrectomy and control groups; however, there are also studies comparing changes in the gut microbiome before and after gastrectomy in patients with gastric cancer. Liang et al. [25] compared fecal samples collected within one week before surgery with the initial fecal samples post-surgery from six patients who underwent distal gastrectomy (one with Billroth II anastomosis and five with Roux-en-Y gastrojejunostomy). The diversity index indicated no significant differences between preoperative and postoperative samples. This suggests that observed microbial diversity changes in other studies might not occur immediately after surgery but rather over a relatively extended period.

GASTRIC MICROBIOME AFTER GASTRECTOMY

In the study by Tseng et al., [26] gastric tissues were obtained preoperatively and approximately two years postoperatively from six patients who underwent subtotal gastrectomy for gastric cancer. The results illustrated an upsurge in the bacterial diversity index after surgery compared to the preoperative levels. Before surgery, *Ralstonia* and *Helicobacter* were relatively abundant, whereas after surgery, the relative abundance of *Streptococcus* and *Prevotella* increased. This coincides with clinical knowledge indicating the tendency of *H. pylori* infection to spontaneously diminish after surgery [27]. Moreover, this aligns with research findings suggesting the migration of oral bacteria from the mouth to the intestines post-surgery, which influences the gut microbiome [18].

In another study by Imai et al., [28] alterations in the microbial composition of gastric fluid after gastric cancer surgery were investigated. The study involved seventy-one patients who

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underwent partial gastrectomy for gastric cancer (40 underwent Billroth I anastomosis, and 31 underwent Roux-en-Y gastrojejunostomy). Gastric fluid samples were collected both preoperatively and six months postoperatively. The observed operational taxonomic units and the Shannon index exhibited a reduction post-surgery, signifying decreased diversity after gastric surgery. Postoperative bacterial taxa commonly observed included *Streptococcus*, *Prevotella 7*, *Lactobacillus*, *Veillonella*, and *Actinomyces*. Additionally, the detection rate of *H. pylori* in the gastric fluid decreased from 43% before surgery to 28% after surgery. A comparative analysis based on the anastomosis method (Billroth I anastomosis vs. Roux-en-Y gastrojejunostomy) did not reveal any significant differences in microbiome diversity. Similar to the changes observed in the gastric mucosal microbiome, the microbiome in the gastric fluid was significantly altered after surgery compared with the preoperative state.

ORAL MICROBIOME AFTER GASTRECTOMY

Recent compelling research has shed light on alterations in the salivary microbiome after gastric cancer surgery. Komori et al. [29] analyzed saliva and gastric fluid samples derived from 63 patients who underwent gastrectomy for gastric cancer, both preoperatively and around 6 months postoperatively. Post-gastrectomy, the salivary microbiome exhibited an increase in the relative abundance of *Lactobacillus* and *Howardella*, while *Actinomyces*, *Fusobacterium*, *TM7x*, and *Butyrivibrio* decreased. Intriguingly, these shifts in saliva mirrored those observed in gastric fluid. There was an elevation in the relative abundance of *Lactobacillus* and a reduction in *Fusobacterium*, *TM7x*, and *Butyrivibrio* in gastric fluid after gastrectomy compared to preoperative levels. Prior studies suggested that the oral microbiome might influence the intestine through the stomach after subtotal gastrectomy. However, evidence illustrating its direct effect due to gastric surgery was lacking. This study confirmed that oral microbiota is indeed influenced by gastric surgery [29], opening up the possibility of its association with systemic diseases [30]. Several factors might elucidate the changes observed in the oral microbiome post-gastrectomy. Firstly, patients undergoing gastric surgery might experience increased gastric acid or bile reflux, influencing the types of microbes that thrive in the oral cavity [31,32]. Similarities in microenvironmental conditions, such as pH levels, induced by gastric acid or bile reflux, may account for resemblances in the composition of gastric and oral microbiomes. Bacterial like *Streptococcus*, *Haemophilus*, *Prevotella*, and *Veillonella* are frequently observed in both the esophagus and oral cavity of individuals with gastroesophageal reflux disease [4,5]. Secondly, apart from its role in treating gastric cancer, gastrectomy is also utilized for obesity treatment. Weight loss, hormonal alterations, and changes in the metabolome due to gastric surgery can potentially impact the oral microbiome [11,33]. Notably, documented changes in the oral microbiome have been observed in patients undergoing bariatric surgery [33].

In summary, the comprehensive outcomes of these studies indicate that gastrectomy influences the oral, gastric, and gut microbiomes through surgery-induced anatomical and physiological changes. It is likely that these effects manifest over extended periods.

GUT MICROBIOME AFTER ANTICANCER TREATMENT

The impact of anticancer treatment on the composition of the gut microbiome appears to be less significant than that of surgery. Chen et al. [34] analyzed fecal samples from 157 gastric

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cancer patients, categorizing them based on whether they underwent surgery or received anticancer treatment, which included chemotherapy and immunotherapy. Notably, patients who underwent surgery exhibited a substantial difference in fecal microbiome composition compared to those who didn't. Specifically, there was a higher relative abundance of Bacteroidetes, Bacillota, Actinomycetota, and Fusobacteria in patients who underwent surgery, aligning with previous research findings. Conversely, patients who received anticancer treatment displayed no significant variance in fecal microbiome composition compared to those who did not. Alpha-diversity indicators like the Chao1 and Shannon indices exhibited no discernible differences concerning anticancer treatment, and beta-diversity did not present significant variances.

However, notable differences in gut microbiome composition emerged between patients with gastric cancer who responded to anticancer treatment and those who did not (**Fig. 2**). Han et al. [35] reported differences in fecal microbiome composition among patients with unresectable gastric cancer, based on their response or lack thereof to chemotherapy or immunotherapy. This study encompassed 152 patients with human epidermal growth factor receptor 2-negative unresectable gastric cancer. Of these, 39 received chemotherapy (XELOX regimen) alone, 76 received anti-programmed death-ligand 1 (PD-L1)/programmed cell death-1 (PD-1) immunotherapy alone, and 37 received a combination of XELOX and anti-PD-L1/PD-1 immunotherapy (with the treatment method for one patient unknown) [35]. Patients who responded to chemotherapy had higher relative abundances of *Dialister*, *Enterobacter*, and *Citrobacter* spp., whereas those who responded to immunotherapy had higher relative abundances of *Lactobacillus*, *Erysipelotrichaceae*, *Ruminococcus*, and *Eubacterium*. Patients who responded to a combination of chemotherapy and immunotherapy showed higher relative abundances of *Bilophila*, *Clostridiales Incertae Sedis XIII*, and *Flavonifractor*. Bacterial taxa associated with treatment response can be used to predict prognosis. For instance, in the study by Han et al., [35] *Citrobacter* and *Enterobacter* were correlated with the progression-free survival of patients receiving chemotherapy, *Lactobacillus* and *Erysipelotrichaceae* with immunotherapy, and

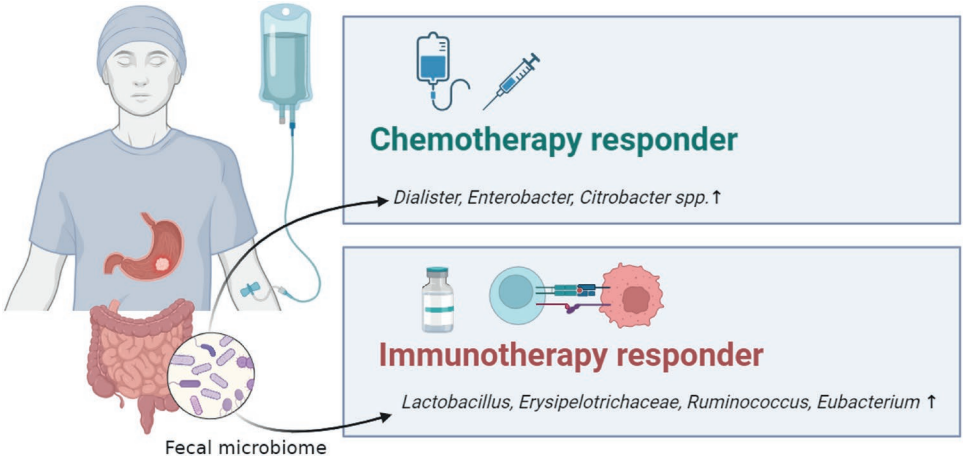

Fig. 2. Association between the gut microbiome and treatment responsiveness in patients with gastric cancer. However, the effect of anticancer treatments on the gut microbiome remains unclear. However, there appears to be an association between the composition of the gut microbiome in patients with gastric cancer and responsiveness to chemotherapy or immunotherapy. Patients who responded to chemotherapy exhibited a higher relative abundance of *Dialister*, *Enterobacter*, and *Citrobacter* spp. than non-responsive patients. In contrast, immunotherapy-responsive patients showed a higher relative abundance of *Lactobacillus*, *Erysipelotrichaceae*, *Ruminococcus*, and *Eubacterium* than non-responsive patients. These findings suggest the potential utility of the gut microbiome in predicting treatment response and prognosis in patients with gastric cancer.

https://doi.org/10.5230/jgc.2024.24.e4

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Flavonifractor plautii with the progression-free survival of patients receiving both chemotherapy and immunotherapy. Notably, categorizing all participants based on high or low relative abundance of *Lactobacillus* indicated that those with a high relative abundance of *Lactobacillus* were more likely to respond to chemotherapy or immunotherapy.

BENEFICIAL EFFECTS OF PROBIOTICS IN PATIENTS WITH GASTRIC CANCER

Utilization of the gastrointestinal microbiome for gastric cancer treatment requires further research; however, recent studies have drawn attention to the potential benefits of probiotics in recovery after gastric cancer surgery [36,37]. In 2019, Zheng et al. [36] reported that the administration of probiotics to patients with gastric cancer undergoing partial gastrectomy reduced postoperative inflammation and enhanced immune responses. The probiotics used by Zheng et al. [36] included *Bifidobacterium infantis*, *Lactobacillus acidophilus*, *Enterococcus faecalis*, and *Bacillus cereus*. Drugs were administered orally 3–5 days after partial gastrectomy for a maximum of 6–7 days. After randomly assigning 100 subjects to receive either probiotics or a placebo, the probiotics group exhibited a decreased inflammation index (leukocytes) while showing an enhanced immunity index (lymphocytes) and nutritional indices (albumin and total protein) compared to the placebo group. Analysis of fecal samples after probiotic or placebo administration revealed no significant differences in the number of observed species or the Shannon index between the two groups. However, the probiotic group exhibited an increased relative abundance of *Bacteroides*, *Faecalibacterium*, and *Akkermansia*, along with a decreased relative abundance of *Streptococcus* compared to the placebo group. In a subsequent study by the same research group, Cao et al. [37] presented a new study on probiotics containing *Clostridium butyricum*. *C. butyricum* promotes the proliferation and development of intestinal probiotics, inhibits the growth of pathogenic bacteria and increases serum immunoglobulins [38,39]. Cao et al. [37] randomized 100 patients after gastric cancer surgery to receive *C. butyricum* or placebo orally for up to 21 days. The *C. butyricum* group exhibited decreased levels of leukocytes, neutrophils, interleukin (IL)-1β, IL-6, and tumor necrosis factor-α while showing increased levels of immunoglobulins, lymphocytes, albumin, and total protein compared to the placebo group. Fecal analysis revealed higher relative abundances of *Bacteroides*, *Faecalibacterium*, and *Gemmiger*, and lower relative abundances of *Streptococcus*, *Desulfovibrio*, and *Actinomyces* in the *C. butyricum* group. Although the oral administration of probiotics after gastric cancer surgery does not directly target or prevent cancer recurrence, it seems to alleviate postoperative inflammation, bolster immune responses, and contribute to maintaining a healthy gut microbiome.

CONCLUSIONS

Thus far, we have examined the intricate patterns of changes within the gastrointestinal microbiome following gastric cancer treatment. Notably, gastrectomy for gastric cancer instigates considerable anatomical and physiological modifications, resulting in shifts in gastrointestinal oxygen levels, pH levels, bile acid flow, and hormonal dynamics. These alterations lead to an enlargement of the oral cavity, increased aerotolerance, and a rise in bile acid-transforming bacteria within the intestines. Furthermore, partial gastrectomy exerts an influence on the gastric microbiome, extending its impact to the oral microbial community. Notably, the modifications in the gut microbiome post-gastrectomy seem

https://doi.org/10.5230/jgc.2024.24.e4

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to manifest not immediately after the surgery but over a prolonged period, persisting for an extended duration. Contrarily, while the effect of chemotherapy or immunotherapy on the gut microbiome appears relatively restricted, there exists a discernible association between the gut microbiome and the response to these treatments. This underscores the potential of leveraging the gut microbiome for predicting responses to such therapies. Despite the current challenges in the direct application of the gut microbiome in gastric cancer treatment, the introduction of probiotic supplementation post-gastric cancer surgery demonstrates promise in mitigating severe inflammatory responses, boosting immune functionality, and enhancing nutritional indicators. Consequently, the prospective role of probiotics in expediting postoperative recovery holds significant promise for future advancements in patient care.

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