Functional constipation as a neglected condition in laryngectomized patients

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ABSTRACT

Background/Aims: When considering the quality of life of patients who undergo total laryngectomy, constipation problems are often overlooked. This study aims to determine whether surgical or concurrent chemoradiotherapy treatments matter in the development of functional constipation in patients with advanced-stage laryngeal cancer.

Materials and Methods: Patients without presurgical constipation (according to Rome IV) who were treated with either surgery (n=30) or chemoradiation (n=25) were evaluated for constipation development. Interim evaluation and recommendations were made on the 3rd month. On the 3rd and 6th months, the frequency of constipation between groups was compared using the Rome IV criteria and European Organization for Research and Treatment of Cancer Quality of Life Scale-C30 constipation symptom score.

Results: On the 3rd month, the frequency of constipation was higher in the surgery group than in the chemoradiation group (76.7% vs. 28%, p<0.001). On the 6th month, although still higher, the frequency of constipation decreased following the recommendations in laryngectomized patients (56.7% vs. 36%, p=0.17). C30 Constipation "yes/no" inquiry failed to detect 11 (36.6%) and 8 (26.6%) laryngectomized patients with constipation on the 3rd and 6th months, respectively.

Conclusion: Constipation is more frequent and develops in the early period of postlaryngectomy. Patients seem to benefit from additional special rehabilitation recommendations. Constipation-prone laryngectomized patients should be screened with the Rome IV criteria, which effectively detect constipation.

Keywords: Laryngectomy, constipation, Rome IV, quality of life, cancer, rehabilitation

INTRODUCTION

Constipation is one of the most common digestive disorders affecting 16%-24% of adults (1, 2). The incidence of constipation increases with age, and it is more frequent in females, being even more prevalent particularly in hospitalized elderly individuals (2, 3). Constipation may manifest as a primary disorder or can develop caused by other underlying causes. Reduced physical activity, use of certain drugs, poor socioeconomic conditions, depression, or any condition causing excessive stress are the known factors associated with constipation (4). The prevalence of constipation, which may occur secondary to various causes, also increases in the presence of a severe disease, particularly advanced-stage cancer (5). The prevalence has increased from 23% to 55% in advanced cancers and in terminally ill patients (6).

Despite the ongoing advances in the surgical treatment of laryngeal cancers, total laryngectomy (TL) remains the treatment of choice in advanced-stage laryngeal malignancies. In TL, the larynx is removed, and the respiration system ended with a permanent tracheostoma. The quality of life is impaired in patients who undergo TL because the basic functions, such as breathing, speech, swallowing, and smell, are affected. The affected functions and the reduced quality of life cause serious problems during the post-treatment period (7, 8). When considering the quality of life of patients with cancer, the constipation or defecation characteristics are often overlooked (7, 9).

Using radiopaque markers, Ugur et al. showed that compared with those in patients with benign laryngeal disease, colonic transport time is prolonged and permanent loss of glottic closure increases the prevalence of functional constipation in laryngectomized patients (9).

Constipation may develop in laryngectomized patients because of various reasons; various factors such as dietary changes in the postoperative period, changes in defecation habits, loss of mobility, different drug treatments and exposure to radiotherapy, anxiety, and depression might contribute to developing constipation in this patient group (10). Moreover, constipation can be

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even more common in the advanced stage of cancer than in the earlier stage (11). Therefore, selecting patients who are in the advanced stage of cancer may be an appropriate approach for investigating the prevalence and causes of constipation in patients with cancer.

The aim of this study is to 1) determine whether surgical or laryngeal preservation treatments matter in the development of functional constipation in patients with advanced-stage laryngeal cancer; 2) to evaluate the relationship between permanent loss of glottic closure and constipation; 3) to investigate the impact of possible associated factors that may cause constipation.

MATERIALS AND METHODS

Patient selection

This study evaluated patients who were admitted to our institution between January 2015 and January 2019 with the diagnosis of advanced-stage laryngeal cancer and who were treated with either TL or concurrent chemoradiation. Concurrent chemoradiation is a laryngeal preservation protocol and is an alternative treatment option to TL in patients with appropriate indication (without cartilage invasion and extralaryngeal spread). The exclusion criteria were as follows: presence of constipation according to the Rome criteria before treatment (12), coexistence of known chronic diseases or diseases detected during the study that possibly contribute to developing constipation (such as diabetes, hypothyroidism, and Parkinson's disease), presence of electrolyte imbalance (such as hypercalcemia and hypokalemia), taking medication that could cause constipation, and incomplete data. In the chemoradiation group, patients with tracheostomy or those who underwent tracheostomy during treatment were also excluded. Ultimately, we included 30 patients who underwent TL and postoperative radiotherapy and 25 patients who underwent chemoradiation. The local ethics committee approved this study. Information regarding the purpose and methods of the study was explained to the patients, who eventually provided individual informed consents.

Study design

All patients who participated in this study were informed about the possibility of developing constipation and the ways on how to deal with it. In both groups, same dietary recommendations and exercise program (regular consumption of fruits and vegetables, intake of fiber-rich food, and regular light physical activity, such as walking) were provided. During participants' routine follow-up visit in the 3rd month of treatment, the presence of constipation was assessed. A gastroenterologist evaluated those with constipation for possible causes of constipation and then made some additional recommendations, such as visiting the restroom twice a day (30 min after regular meals and waiting in the sitting position for a while) and closing the tracheostoma with the finger during straining for laryngectomized patients. Suggestions regarding symptomatic treatment were also made. Patients were re-assessed at their 6th month routine follow-up visit.

Constipation frequency was compared between the TL and chemoradiation groups on the 3rd and 6th months. The Rome criteria (12, 13) and European Organization for Research and Treatment of Cancer Quality of Life Scale-C30 (EORTC QLQ-C30) constipation symptom score (14) were used to evaluate constipation. In addition, we assessed whether the anxiety and depression scale scores differed between the two treatment groups.

Outcome criteria

Rome criteria

Functional constipation was assessed by Rome criteria (Rome III [at the beginning of the study] and Rome IV; version updated in 2016 and after 2016, respectively) in a standardized manner (12, 13). Considering that no difference was found between these criteria in terms of the definition of functional constipation, all results were evaluated under the heading of Rome IV criteria.

According to Rome III and IV criteria, the presence of symptoms during the last 3 months, with the onset of symptoms occurring at least 6 months prior, is defined as functional (chronic) constipation, whereas an assessment of over 3 months as per the definition of chronic constipation without the requirement of 6 months of symptom onset is defined as subchronic constipation (modified Rome III criteria) (15). The results of patients who did not experience constipation before treatment according to the Rome criteria were examined; those who met the criteria in the 3rd and 6th month post-treatment evaluations were categorized as having subchronic and chronic constipation, respectively.

EORTC QLQ-C30 constipation symptom scale

The EORTC QLQ-C30, which is a globally used quality-of-life scale for patients with cancer, is not specific for laryngeal cancer (14). It contains 30 items under the following three subdimensions: general well-being, functional difficulties, and symptom control. As part of symptom evaluation, constipation is also assessed with the

question "Have you been constipated in the last week?" and scored from 1 to 4 (as not at all, a little, quite a bit, and very much, respectively). As constipation complaint increases, the constipation symptom score also increases (between 0 and 100) (16).

In addition, we developed the C30 Constipation (yes/no) inquiry to test its ability to detect any patient with constipation based on the Rome criteria. Patients responding "not at all" to the question on constipation according to the EORTC QLQ-C30 were regarded as having no constipation, whereas those responding "a little," "quite a bit," or "very much" were regarded as having constipation. Its ability to detect patients with constipation was evaluated according to the Rome criteria.

Beck Depression Inventory (BDI)

The BDI measures the physical, emotional, and cognitive symptoms observed during depression (17). It is a self-assessment scale that includes 21 symptom categories, with 63 as the highest possible score. The higher the total score, the more severe the depression felt. Its reliability and validity have been reported in a Turkish population by Hisli (18).

Beck Anxiety Inventory (BAI)

The BAI measures the frequency of anxiety symptoms experienced by an individual (19). It is a Likert-type self-assessment scale comprising 21 items scored between 0 and 3. The higher the total score, the higher the anxiety experienced by the person (0-7, 8-15, 16-25, and 26-63 points=minimal, mild, moderate, and severe anxiety, respectively). Its reliability and validity have been reported in a Turkish population by Ulusoy et al. (20).

Table 1. Patient characteristics based on treatment types.

Variables	Total Laryngectomy	Chemoradiation
Age; mean±SD (median), years	61.03±5.84 (60.50)	60.08±6.23(60)
Sex, n (%)		
Male	29 (96.7)	24 (96)
Female	1 (3.3)	1 (4)
Marital Status, n (%)		
Single	1 (3.3)	-
Married	26 (86.7)	22 (88)
Widowed	3 (10)	3 (12)
Employment Status, n (%)		
Employed	17 (56.7)	23 (92)
Unemployed	13 (43.3)	2 (8)
Tumor Stage, n (%)		
III	21 (70)	23 (92)
IV	9 (30)	2 (8)

SD: Standard deviation; n: Patient number

Statistical analysis

Data were analyzed using the SPSS software version 22.0 (IBM Corp., Armonk, NY, USA). The normality of data was tested by the Shapiro–Wilk test and graphical examinations. For nonparametric data and small sample size, nonparametric tests were used. Categorical variables are expressed as numbers (percentage), and continuous variables are expressed as mean±standard deviation (SD) as well as median±interquartile range (IQR). Continuous variables were compared between the groups by Mann–Whitney U-test. Categorical variables between the groups were analyzed using the chi-square test. In addition, $p<0.05$ was considered statistically significant.

RESULTS

Out of the 62 patients with advanced-stage laryngeal cancer, 34 underwent TL with bilateral neck dissection and postoperative radiotherapy (1.8-2.0 Gy per fraction, 5 days per week, with a total dose of 54-60 Gy), and 28 underwent chemoradiation therapy (2 cycles of cisplatin (Cisplatin-Koçak, Koçak Farma, Tekirdağ, Turkey) (75-100 mg/m^2) and concurrent radiation therapy (2.12 Gy per fraction, 5 days per week, with a total dose of 70 Gy). However, four patients in the TL group (because of missing data) and three in the chemoradiation group (two because of tracheotomy and one because of missing data)

Table 2. Presence of functional constipation according to Rome IV criteria based on treatment types

	Total Laryngectomy (n=30)	Chemoradiation (n=25)	p
Rome IV Criteria			
Pretreatment	0	0	
3rd-month follow-up, n (%)	23 (76.7)	7 (28)	<0.001*
6th-month follow-up, n (%)	17 (56.7)	9 (36)	0.117

3rd-month follow-up results represent subchronic constipation

6th-month follow-up results represent chronic constipation

Chi-square test

*p<0.001

were excluded. Thus, 30 TL patients with a mean age of 61.03±5.84 years and 25 chemoradiation patients with a mean age of 60.08±6.23 years were included (p=0.59), and their data were evaluated subsequently. Table 1 summarizes the sociodemographic and clinical characteristics of patients.

On the 3rd month of evaluation, the frequency of constipation was higher in the TL group than in the chemoradiation group, with a significant difference observed between them (76.7% vs. 28%, p<0.001; Table 2).

After interim evaluation and recommendations, eight TL patients with subchronic constipation improved, with no constipation on the 6th month; conversely, two TL patients without previous constipation diagnosis developed constipation on the 6th month. In the chemoradiation group, two patients improved, whereas five patients developed constipation on the 6th month.

On the 6th month of evaluation, the frequency of constipation decreased in the TL group and increased in the chemoradiation group. Although the difference be-

Table 3. Presence of constipation based on Rome IV criteria and C30 constipation (yes/no) inquiry in laryngectomized patients.

Rome IV Criteria		C30 Constipation (yes/no)		Total Cases based on Rome IV Criteria, n (%)
		Yes	No	
3rd-month follow-up				
Subchronic constipation	Yes	12	11	23 (76.7)
	No	2	5	7 (56.7)
6th-month follow-up				
Chronic constipation	Yes	9	8	17 (56.7)
	No	2	11	13

C30 Constipation (yes/no) inquiry: Based on the question in the C30 constipation scale "Have you been constipated in the last 1 week?"; those who responded "never" are categorized as NO, whereas those who responded "sometimes, often, or always" are categorized as YES.

Table 4. C30 constipation symptom, BAI and BDI scores based on treatment types.

Variables	Total Laryngectomy		Chemoradiation		
	mean±SD	median (IQR)	mean±SD	Median (IQR)	p
C30 Constipation					
Pretreatment	17.78±24.34	0.00 (33.33)	8.00±17.43	0.00 (0.00)	0.075
3rd-month follow-up	20.00±25.67	0.00 (33.33)	24.00±28.09	0.00 (50.00)	0.628
6th-month follow-up	14.44±20.87	0.00 (33.33)	16.00±25.68	0.00 (33.33)	0.944
BAI					
Pretreatment,	13.53±10.06	12.00 (14.80)	16.48±5.84	16.00 (10.5)	0.048*
3rd-month follow-up	8.63±8.38	4.50 (11.30)	11.52±5.08	10.00 (7.00)	0.009**
6th-month follow-up	6.10±6.34	4.00 (3.80)	8.16±4.05	8.00 (6.00)	0.006**
BDI					
Pretreatment	17.70±8.14	17.50 (11.30)	17.16±3.70	17.00 (5.00)	0.826
3rd-month follow-up	11.93±9.50	10.50 (11.30)	19.20±4.90	19.00 (7.5)	0.001**
6th-month follow-up	7.40±6.70	5.00 (9.50)	10.72±4.27	11.00 (7.5)	0.005**

C30 Constipation: Constipation symptom scores for the European Organization for Research and Treatment of Cancer Quality of Life Scale-C30; BAI: Beck Anxiety Inventory; BDI: Beck Depression Inventory; SD: standard deviation; IQR: Interquartile range

Mann–Whitney U test

*p<0.05

**p<0.01

tween the groups was insignificant, the frequency of constipation remained higher in the TL group than in the chemoradiation group on the 6th month (56.7% vs. 36%, p=0.117; Table 2).

The ability of C30 Constipation "yes/no" inquiry to detect any patient with constipation was evaluated according to the positive cases with Rome criteria. The C30 Constipation "yes/no" inquiry failed to detect 11 (36.6%) TL patients with constipation on the 3rd month and 8 (26.6%) TL patients with constipation on the 6th month (Table 3).

When the averages of the EORTC QLQ-C30 constipation symptom score were examined, no significant difference was observed between the groups at baseline and on the 3rd and 6th months after treatment (p=0.075, p=0.628, and p=0.944, respectively; Table 4).

When the BDI scores were compared, the baseline scores of the groups were not significantly different; however, the scores were significantly higher in the chemoradiation group on the 3rd and 6th months after treatment (p=0.826, p=0.001, and p=0.005, respectively; Table 4).

Meanwhile, the BAI scores revealed mild and moderate anxiety in the TL and chemoradiation groups, respectively, during the pretreatment period. On the 6th month after treatment, anxiety decreased to minimal and mild in the TL and chemoradiation groups, respectively. In all evaluations, including those conducted in the pretreatment period, anxiety was more prominent in the chemoradiation group than in the TL group, with a statistically significant difference (p=0.048, p=0.009, and p=0.006, respectively; Table 4). According to the medical records, patients received psychotherapy support but did not receive medical treatment for anxiety and depression.

Based on the Rome criteria, constipation symptom characteristics in the TL group were evaluated. Accordingly, the three most commonly reported Rome criteria symptoms on the 3rd month were having less than three defecations per week, feeling of incomplete evacuation, and feeling of straining during defecation, whereas those reported on the 6th month were having less than three defecations per week, lumpy or hard stool, and feeling of straining during defecation. Symptom frequencies decreased on the 6th month compared with those on the 3rd month (Table 5).

The presence of constipation was evaluated in relation to age. Functional constipation was identified in seven patients aged >65 years in the TL group and in nine patients aged >65 years in the chemoradiation group; in other words, all patients with constipation in the chemoradiation group on the 6th month aged >65 years (41.17% vs. 100%).

In the investigation on the use of any drug that had a constipation-inducing effect, no difference was observed between the groups and between patients with constipation according to medical records and patient statements.

DISCUSSION

The findings of the present study indicate that constipation is more frequent and develops early in laryngectomized patients than in those who underwent chemoradiation therapy. Patients appear to benefit from

Table 5. Characteristics of reported constipation symptoms in laryngectomized patients.

Criteria of at least 25% of defecation	Frequency of Symptoms, n (%)		
	3rd-month	6th-month	p
Straining during defecation	16 (53.3)	8 (26.7)	0.03*
Lumpy or hard stool	15 (50)	14 (46.7)	0.79
Incomplete evacuation	18 (60)	4 (13.3)	<0.001**
Sensation of anorectal obstruction/blockage	8 (26.7)	3 (10)	0.09
Manual maneuvers to facilitate defecation	9 (30)	4 (13.3)	0.11
Fewer than 3 defections per week	22 (73.3)	16 (53.3)	0.005**

Chi-square test

*p<0.05

**p<0.01

rehabilitation recommendations provided for constipation, which was detected in the early period.

Permanent loss of laryngeal function negatively impacts the quality of life of patients who undergo TL by negatively affecting several physiological processes, including nutrition, speech, smell, and breathing (7, 21, 22). Loss of glottic closure, which is critical for the initiation of voluntary defecation, also leads to the development of constipation (23).

Among the functions that are adversely affected by laryngeal function loss, constipation is one of the least studied. In a cross-sectional study, laryngectomized patients who were evaluated in the first 2 postoperative years underwent slow colonic transit constipation, which was determined using the Rome II criteria (9). In the same study, without any preoperative data, patients with laryngeal cancer were compared with those without. In the present study, patients without presurgical constipation were evaluated for constipation development in the first 6 postoperative months. In addition, the comparison of groups with a similar disease stage, where both groups received radiotherapy, provided a more homogenous assessment of a possible causal link between constipation and TL. Moreover, they were informed about the possibility of developing constipation from the beginning of their treatment. However, patients who underwent TL were more prone to develop constipation.

The Rome criteria are the gold standard test for constipation examination. They were developed in 1992 to objectively identify and detect functional diseases in the digestive system, especially constipation, and are regularly revised. These criteria were last revised in 2016 and are known as Rome IV criteria. Rome IV criteria differ from Rome I criteria, wherein Rome IV allows the differential diagnosis of outlet obstruction; it also differs from Rome II criteria, wherein an occasional loose stool does not exclude functional constipation in Rome IV. However, Rome IV criteria do not differ from Rome III criteria in terms of functional constipation definition (24). Therefore, no distinction was made between the study patients evaluated using the Rome III criteria and those evaluated using the Rome IV criteria.

The EORTC QLQ-C30 scale, which has been used worldwide, was developed to evaluate the quality of life of patients with cancer, and one of the symptoms questioned in this scale is constipation (8, 14, 25). However, patients are only asked whether they were constipated in the last week, and answers from "not at all" to "very much" are recorded. Constipation is defined differently by both patients and physicians. Therefore, merely asking the patients "Have you been constipated last week?" is insufficient to assess the presence of constipation. Indeed, in our present study, this scale was insufficient in detecting patients who had constipation based on the Rome criteria.

The impact of constipation in patients with cancer should not be underestimated. Constipation can result in bloating, abdominal pain, nausea, and even vomiting, thereby impairing food intake and treatment compliance of the patients and ultimately leading to weight loss and dehydration. Therefore, it can adversely affect the quality of life, treatment compliance, and healing process of patients with cancer. Hence, earlier detection of constipation and its management are crucial in patients with cancer.

Various causes can contribute to the development of constipation in patients with cancer, including underlying disease, age, mood swings, radiotherapy, decreased mobility, and the use of numerous medications that can cause constipation (26). In the present study, the frequent occurrence of constipation in laryngectomized patients regardless of age supports the idea that the dynamic change caused by surgery is an independent risk factor for the development of functional constipation.

Furthermore, depression and anxiety affect the quality of life in patients with cancer; they may cause changes in patients' bowel habits, leading to constipation (27, 28). However, the insight into whether these mood swings differ between patients undergoing chemoradiation therapy and those undergoing TL remains unclear. During the preoperative period, depression and anxiety scores were significantly higher in the chemoradiation group than in the TL group; this significant difference persisted in the evaluations performed on the 3rd and 6th months. Therefore, in terms of functional constipation frequency, the presence or severity of anxiety and depression did not contribute to the significant increase observed in the TL group as much as the effect of permanent loss of glottic closure.

Radiotherapy can result in constipation via different mechanisms, including dysphagia, nausea and vomiting, esophagitis or mucositis, and the deteriorating effects of pain or drugs used for pain control on intestinal function and habits (29). In the present study, both patient

groups underwent radiotherapy, with a higher dose and a longer duration in the chemoradiation group than in the TL group. However, the frequency of constipation, which was verified using the Rome criteria, was far less in the chemoradiation group than in the TL group. Therefore, radiotherapy, which is an important risk factor for constipation, contributed less to the development of functional constipation than the permanent loss of glottic closure, at least during the early period.

Effective bowel function and normal defecation are indispensable for a normal healthy life. However, they are often considered as unimportant topics and do not receive sufficient attention from patients, relatives, and physicians during the treatment and follow-up of a life-threatening disease, such as laryngeal cancer.

The aim of constipation management is to normalize bowel movements, enable soft stool defecation, ensure defecation at least thrice a week without difficulty, and improve the quality of life of the patient without serious side effects. Training the patient on dietary changes, behavioral changes, and laxative use is the basis of treatment (10, 30). In the present study, all patients were provided with recommendations on dietary and lifestyle changes prior to the treatment to reduce the constipating effect caused by possible dietary changes. All patients diagnosed with constipation 3 months after treatment were recommended to undergo bowel rehabilitation. In the TL group, closing the tracheostoma during defecation is recommended to aid in straining; by using this method, patients could better perform the Valsalva maneuver, which could not be effectively performed because of the loss of glottic closure. After these recommendations were provided on the 3rd month, constipation incidence decreased on the 6th month in the TL group but increased in the chemoradiation group. Although similar recommendations were given to patients with constipation in both groups, the lack of improvement in the chemoradiation group can be explained by the fact that constipation observed in the TL group was mostly caused by surgery and patients benefited from stoma closure during straining. Radiotherapy regimen, which was given in different doses and durations, and the presence of persisting anxiety and depression may have admittedly played a role in the lack of improvement in the chemoradiation group. Furthermore, based on constipation symptom characteristics, the significant decrease in straining during defecation and incomplete evacuation in TL patients at 6 months are the effects of surgery-induced constipation.

Meanwhile, this study has several limitations. It was conducted at a single center and performed with relatively few patients; thus, generalization of the study results may not be achieved. The patients' statements were considered to be sufficient to track dietary compliance and bowel rehabilitation practices; however, different control methods were not applied. Furthermore, the follow-up period was not long, and the study was not designed to directly solve the problem and assess the impact on the quality of life. Thus, further multicenter studies with a large number of patients and long-term follow-up are necessary to demonstrate the effectiveness of such programs.

In conclusion, several factors may contribute to the development of functional constipation in patients with advanced-stage laryngeal cancer. However, the most important factor during the early postoperative period is the inability to effectively perform the Valsalva maneuver because of the permanent loss of glottic closure secondary to surgical treatment.

The quality of life, treatment compliance, and healing process of patients with cancer may be adversely affected by constipation. Therefore, laryngectomized patients prone to constipation should be screened for constipation development during the early period. When evaluating the presence of constipation, the use of Rome IV criteria may early and effectively detect constipation, whose negative effects on the quality of life are often overlooked.

Ethics Committee Approval: Ethics committee approval was received from the Ethics Committee of Kocaeli University School of Medicine (Decision number: 2014/34).

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