Laryngeal Carcinoma in Patients With Inflammatory Bowel Disease: Clinical Outcomes and Risk Factors

Steffi E. M. van de Ven, MD,* Steffi E. M. van de Ven, MD,* Steffi E. M. van de Ven, MD,* Lauranne A. A. P. Derikx, PhD,† Iris D. Nagtegaal, PhD,‡, Carla M. van Herpen, PhD,§ Robert P. Takes, PhD,¶ Willem J. G. Melchers, PhD,† Marieke Pierik, PhD,‖ Tim van den Heuvel, PhD, Rob H. A. Verhoeven, PhD,‖ Frank Hoentjen, PhD,† and L. H. C. Nissen, PhD,‡‡; on Behalf of the Dutch Initiative on Crohn and Colitis (ICC), Dutch Head and Neck Society, PALGA Group, and IBD/HNC Group

Background: Inflammatory bowel disease (IBD) patients are at increased risk for developing extra-intestinal malignancies, mainly due to immunosuppressive medication. The risk of developing head and neck cancer in immunosuppressed transplant patients is increased. The relation between IBD patients and laryngeal cancer (LC) remains unclear. We aimed (1) to identify risk factors in IBD patients for LC development and (2) to compare clinical characteristics, outcome, and survival of LC in IBD patients with the general population.

Methods: All IBD patients with LC (1993–2011) were retrospectively identified using the Dutch Pathology Database. We performed 2 case–control studies: (1) to identify risk factors, we compared patients with IBD and LC (cases) with the general IBD population; (2) to analyze LC survival, we compared cases with controls from the general LC population.

Results: We included 55 cases, 1800 IBD controls, and 2018 LC controls. Cases were more frequently male compared with IBD controls ($P < 0.001$). For ulcerative colitis (UC), cases were older at IBD diagnosis ($P < 0.001$). Crohn's disease (CD) cases were more frequently tobacco users ($P < 0.001$) and more often had stricturing ($P = 0.006$) and penetrating ($P = 0.008$) disease. We found no survival difference. Immunosuppressive medication had no impact on survival.

Conclusions: Male sex was a risk factor for LC in IBD patients. Older age at IBD diagnosis was a risk factor for UC to develop LC. Tobacco use and stricturing and penetrating disease were risk factors for LC development in CD patients. Inflammatory bowel disease was not associated with impaired survival of LC. Immunosuppressive medication had no influence on survival.

Key Words: inflammatory bowel diseases, head and neck cancer, laryngeal carcinoma, immunosuppressive therapy

INTRODUCTION

Inflammatory bowel disease (IBD) patients are at increased risk for developing colorectal cancer (CRC) due to prolonged chronic inflammation.¹,² In IBD patients, there is also an increased risk of developing extra-intestinal malignancies (EIMs), in part due to the use of immunosuppressive medication.³,⁴ This can be the result of DNA damage and decreased immune surveillance.³,⁴ Due to the potential cancer risk, there is rising concern about the use of immunosuppressive medication in IBD patients.¹ Moreover, the use of immunosuppressive medication in IBD patients is associated with an increased risk of developing skin cancer and lymphoma.⁷,⁸

In other patient cohorts with immunosuppressive medication, such as in transplant patients or in patients with rheumatoid arthritis, the increased cancer risk is well established.⁹,¹⁰ Both tumor growth and metastasis development can accelerate as a consequence of immunosuppressive medication, resulting in reduced survival rates.¹⁰ For example, I study reported that the incidence of head and neck cancer (HNC) in transplant patients was doubled compared with the general population, with worse survival.¹¹ Although human papillomavirus (HPV) is associated with the development of cancer in the (oro)pharynx, HPV infection is not a major cause of laryngeal cancer (LC).¹²,¹³
The prevalence of LC is up to 3.0% in transplant patients on immunosuppressive medication. No specific risk factors for LC development have been identified in transplant patients, probably due to the small number of cases. Only a few articles have been published about the HNC prevalence in IBD patients on immunosuppressive medication. Although the risk of developing oral cavity carcinoma (OCC) and oropharyngeal carcinoma (PC) in IBD patients has previously been reported, the occurrence of LC in IBD patients has scarcely been reported in literature. In a series of 404 patients with Crohn’s disease (CD) treated with infliximab, only 1 patient developed LC.

In this study, we aimed to (1) identify risk factors in IBD patients for the development of LC, (2) compare the clinical characteristics, outcome, and survival of IBD patients with LC with those of the general population, and (3) assess whether immunosuppressive medication had an influence on the survival. Given impaired survival in IBD patients with OCC, we hypothesized worse outcome in IBD patients with LC (cases) compared with the general LC population. In addition, we hypothesized worse survival in cases treated with immunosuppressive medication compared with cases who did not use immunosuppressive medication. We performed 2 population-based case–control studies with cases and IBD controls, and with cases and LC controls.

METHODS

Study Design

Two retrospective population-based case–control studies were performed:

1. To identify risk factors for the development of LC in IBD patients, IBD patients with LC (cases) were compared with the general IBD population (controls).
2. To compare clinical characteristics, outcome, and survival of the LC population between those with IBD and the general LC population, IBD patients with LC (cases) were compared with the general LC population (controls).

Case Selection

To identify all Dutch IBD patients with LC (cases), a search was performed using the national pathology database PALGA. PALGA is the Dutch nationwide network and registry of histo- and cytopathology. The search was performed between January 1, 1993, and December 31, 2012. Search terms for IBD (“ulcerative colitis” or “Crohn’s disease” or “indeterminate colitis” or “chronic idiopathic inflammatory bowel disease”) were combined with search terms for LC (“laryngeal neoplasms” or “cancer of larynx” or “laryngeal cancer”). First, pathology reports were reviewed to make an initial selection of cases. Subsequently, the medical charts of these cases were reviewed.

Patients were included if a diagnosis of both LC and IBD (CD, ulcerative colitis [UC], or IBD-unclassified) was established according to previously published criteria. Exclusion criteria were LC in situ, diagnosis of IBD >3 months after LC diagnosis, no confirmed diagnosis of IBD or LC, diagnosis before 1993 or after 2012, and laryngeal lymphoma. The following data were collected from the medical charts: sex, date of birth, history of smoking and alcohol, medical history, length, and weight.

Furthermore, IBD-specific data were collected, including IBD type based on histopathological evaluation, IBD phenotype, date of IBD diagnosis, use of IBD medication (corticosteroids, 5-aminosalicylates, thiopurines, calcineurin inhibitors, methotrexate, and anti-TNF therapy) and period of medication use, presence of primary sclerosing cholangitis, and type of surgery required for IBD. Characteristics of LC included date of LC diagnosis, tumor stage according to TNM classification (7th edition), history of LC, primary treatment of LC, differentiation grade, recurrence, and survival.

Control Selection

Inflammatory bowel disease controls (case–control study I) were derived from the IBD South Limburg (IBDSL) cohort. The IBDSL cohort consists of adult patients with IBD in South Limburg (the Netherlands) who were diagnosed between 1991 and 2011. Currently, 93% of IBD patients in South Limburg are registered in this cohort. A random selection of 1800 patients was made, as described in detail in a previous publication. Similar data were extracted from both cases and IBD controls, although duration of immunosuppressive medication and smoking and alcohol history were not available for all IBD controls.

LC controls (case–control study II) were derived from the Netherlands Cancer Registry (NCR). The NCR cohort consists of all newly diagnosed patients with cancer in the Southeast of the Netherlands (province of North Brabant and the Northern part of the province of Limburg) since 1989. This cohort is managed by the Netherlands Comprehensive Cancer Organization; >95% of all cancers in this region are registered in this cohort. All LC patients between 1993 and 2012 with LC were selected.

Similar data were extracted from both cases and controls, although the duration of immunosuppressive medication and smoking and alcohol history were not available for all IBD controls.

Statistics

Univariable analysis was used for both case–control studies to compare potential risk factors, LC characteristics, and outcomes between cases and controls. Continuous data were compared with the unpaired 2-sample t test or Mann-Whitney U test. The Pearson chi-square test or Fisher exact test was used to analyze categorical data. Variables with a P value of <0.1 in univariable analyses were included in a multivariable model (model further described per case–control study). A P value of <0.05 was considered statistically significant.
statistical analyses were performed with IBM SPSS statistics, version 24.

Case–Control Study I

A multivariable logistic regression model with backward sampling was used for case–control study I. This model was made separately for UC and CD patients to identify independent risk factors for LC development. This model was adjusted for the duration of follow-up (fixed variable). Follow-up was defined as the time since IBD onset until the date of LC diagnosis, the end of follow-up, or death. Medication use was not included in multivariable analyses because the use of medication, especially in the distant past, might not be reliable and may be different from current regimes. Therefore, another multivariable logistic regression analysis was performed (sensitivity analysis) including patients with IBD in both the case and control groups. Medication use was included in this logistic regression model.

Case–Control Study II

Kaplan-Meier survival curves with log-rank analysis were performed to compare the clinical outcome and survival of IBD patients with LC with those of the general LC population. A separate survival analysis was performed to compare the effect of immunosuppressive medication on the clinical outcome and survival of IBD patients with LC (immunosuppressive medication vs no immunosuppressive medication). Confounder correction was performed with a Cox regression model with forward sampling. A covariate was considered as a confounder when the beta coefficient of the variable of interest changed by 10% or more.

Ethical Considerations

This study was approved by the Privacy Commission and Scientific Council of PALGA and by the Medical Ethics Review Committee of the Radboud UMC, Nijmegen, the Netherlands (registration number 2013/211).

RESULTS

Case Selection

The initial PALGA search yielded 760 potential cases (patients with IBD and head and neck cancer). We excluded 391 patients without LC based on histology reports (Fig. 1). The medical charts of the remaining 369 patients were reviewed. After chart review, 310 patients were excluded, resulting in 55 cases with IBD and LC.

Control selection of the general IBD population, risk factors

In total, 1800 IBD patients from the IBDSL cohort were randomly selected for the identification of risk factors. Univariable comparison between IBD patients with LC (cases) and IBDSL controls (Table 1) showed that cases were older at IBD diagnosis (median, 53.0 vs 39.0 years; \( P < 0.001 \)), were more frequently male (83.6% vs 46.5%; \( P < 0.001 \)), and were more frequently (previous or current) tobacco users (100% vs 62.5%; \( P < 0.001 \)). Crohn’s disease cases more often had stricturing (66.7% vs 14.6%; \( P < 0.001 \)) and penetrating (53.3% vs 11.0%; \( P < 0.001 \)) disease. Additionally, in CD patients, male sex (OR, 3.7; 95% CI, 1.1–12.2; \( P = 0.03 \)) and past or current tobacco use (OR, 4.6; 95% CI, 1.8–11.3; \( P < 0.01 \)) were independent risk factors for the development of LC. In UC patients, male sex (OR, 9.4; 95% CI, 2.8–31.4; \( P < 0.01 \)) and older age at IBD diagnosis (OR, 1.1; 95% CI, 1.0–1.1; \( P < 0.01 \)) were independent risk factors for the development of LC.

A sensitivity analysis (including only patients with an IBD diagnosis since 1991 to reliably evaluate the impact of medication use on LC risk) showed that the use of 5-aminosalicylates (5-ASA; OR, 0.04; 95% CI, 0.01–0.13; \( P < 0.01 \)) is associated with a lower risk of LC for UC patients. Penetrating disease (OR, 5.0; 95% CI, 1.2–20.0; \( P = 0.02 \)) is a risk factor for LC development in CD patients (Table 2).
Control selection of the general LC population: clinical characteristics and outcome

In total, 2018 LC patients from the NCR were selected as controls for the identification of risk factors (Fig. 2). Characteristics of patients with LC (both cases and controls) are shown in Table 3. The median age of patients with LC (controls) was 65 years, and most patients were male (82.8%). TNM stage was in most cases I or II (62.5%), and patients were most often treated with radiotherapy (84.2%). The overall 5-year survival of patients with LC (controls) was 60% (Fig. 3A). No differences in survival between cases and controls ($P = 0.942$) were found, also after adjusting for TNM stage ($P = 0.634$) (Fig. 3A, B).

Survival in IBD Patients With Immunosuppressive Therapy Before LC Diagnosis

Of the 55 patients with IBD and LC, 29 patients had a history of immunosuppressive medication use before diagnosis of LC, whereas 26 patients did not use immunosuppressive medication before LC diagnosis. There was no significant difference in overall survival between these 2 groups ($P = 0.926$).

DISCUSSION

In this nationwide cohort study, we found male sex to be an independent risk factor for LC development in IBD patients,
Both for CD and UC. For UC specifically, older age at IBD diagnosis was a risk factor, and the use of 5-ASA was associated with a lower risk for LC. In CD, past or current tobacco use and stricturing or penetrating disease were independent risk factors for developing LC. We found no impact of immunosuppressive medication on survival after LC diagnosis.

Data regarding the impact of immunosuppressive medication in IBD patients on cancer survival are limited and conflicting. There was no difference in survival for IBD patients with melanoma compared with the general population, whereas IBD patients with gastric cancer, CRC, or OCC showed impaired survival. However, most studies are limited by a retrospective design and carry a risk of bias. Data from transplant patients show that the largest effect on the survival of cancer is observed within the first 2 years after the start of immunosuppressive medication. As the type of immunosuppression, dose, and treatment duration in IBD patients are different, it is uncertain whether these results can be extrapolated to the IBD population. In addition, although transplant patients will use immunosuppressive medication throughout their lives, most IBD patients will switch or discontinue immunosuppressive medication due to side effects or loss of response.

Our results suggest that immunosuppressive medication can be safely used in IBD patients with LC and are therefore reassuring for clinical daily practice. However, they have to be interpreted with caution for several reasons. First, confounding by indication might be present, as most clinicians are reluctant to prescribe immunosuppressive medication to patients at risk for cancer given the possible negative effects. This probably results in mostly low-risk patients receiving immunosuppressive medication. Second, the time relation between tumor development and the start of immunosuppressive medication was unclear due to the retrospective design of this study. Third, because of the limited number of enrolled cases, data could be underpowered to show a significant difference in survival. In the ECCO guidelines, data were limited regarding the effect of immunosuppressive medication on the survival in IBD patients with cancer. No firm conclusions can be drawn about the safety of immunosuppressive medication in IBD patients with LC.

We found older age at IBD diagnosis to be an independent risk factor for the development of LC, particularly in patients with UC. Our results are in line with previous studies of our group and others. One study comparing IBD patients over the age of 60 years with IBD patients aged 18 to 40 years observed a higher rate of cancer in the elderly-onset

### TABLE 2. Multivariable Regression Model After Adjustment for Follow-up: Independent Risk Factors for LC Development

| Model | Variable | Coefficient $\beta$ | Odds Ratio (95% CI) | $P$ |
|-------|----------|----------------------|---------------------|-----|
| Larynx | Ulcerative colitis | Male sex | 2.244 | 9.428 (2.831–31.394) | 0.000 |
| | All cases (n = 35) | Age at IBD diagnosis | 0.058 | 1.060 (1.034–1.086) | 0.000 |
| | Ulcerative colitis | Male sex | 2.255 | 9.532 (2.039–44.571) | 0.004 |
| | Sensitivity analysis (n = 29) | Age at IBD diagnosis | 0.069 | 1.072 (1.036–1.109) | 0.000 |
| | 5-aminosalicylates | -3.321 | 0.036 (0.010–0.131) | 0.000 |
| | Crohn’s disease | Male sex | 1.297 | 3.658 (1.101–12.154) | 0.034 |
| | All cases (n = 18) | Smoking | 1.521 | 4.578 (1.840–11.345) | 0.001 |
| | Crohn’s disease | Smoking | 1.544 | 4.686 (1.681–13.063) | 0.003 |
| | Sensitivity analysis (n = 15) | Penetrating disease | 1.605 | 4.979 (1.238–20.021) | 0.024 |

Similar inclusion periods of IBD diagnosis (since 1991) for cases and controls were used in the sensitivity analysis. Eliminated nonsignificant variables are not shown; only the final model is shown.

![Flowchart of inclusion of NCR controls (general population).](image)
Laryngeal Carcinoma and Inflammatory Bowel Disease

It could be speculated that the phenotype of elderly-onset IBD is associated with a higher risk of cancer.\textsuperscript{28, 39} On the other hand, the high prevalence of tobacco use in LC patients may result in late UC onset and confound our findings. Indeed, we found tobacco use to be an independent risk factor for LC development, especially in CD patients (data lacking for UC). This is consistent with the current literature about risk factors for LC.\textsuperscript{40} Although stricturing disease and penetrating disease in CD patients were independent risk factors for LC development regardless of tobacco use, tobacco use may contribute to ongoing inflammation and result in stricturing and penetrating disease.

To our knowledge, this is the largest systematically collected series of data from LC patients with IBD, which is the major strength of this study. Nonetheless, there are some limitations of our study that need to be addressed. First, the retrospective design resulted in missing data. For example, data regarding the exact time period of immunosuppressive

| Variable | LC patients | NCR patients | Missing, No. | P |
|----------|-------------|--------------|--------------|---|
| Age at diagnosis, median, y | 64.00 | 65.00 | 0/0 | 0.920 |
| Female sex, No. (%) | 9 (16.4) | 347 (17.2) | 0/0 | 0.872 |
| Tumor location, No. (%) | | | | |
| Supraglottis | 12 (21.8) | 697 (35.2) | 0/37 | 0.122 |
| Glottis | 42 (76.4) | 1253 (63.3) | | |
| Subglottis | 1 (1.8) | 31 (1.6) | | |
| Histology, No. (%) | | | | |
| SCC | 53 (96.4) | 1979 (98.1) | 0/0 | 0.297 |
| Differentiation, No. (%) | | | | |
| Good | 5 (15.6) | 222 (14.4) | 23/473 | 0.509 |
| Moderate | 23 (71.9) | 1000 (64.7) | | |
| Poor | 4 (12.5) | 323 (20.9) | | |
| Clinical tumor stage, No. (%) | | | | |
| T stage\textsuperscript{a} | | | | |
| T1 | 26 (47.3) | 793 (40.2) | 0/44 | 0.259 |
| T2 | 19 (34.5) | 598 (30.3) | | |
| T3 | 4 (7.3) | 329 (16.7) | | |
| T4 | 6 (10.9) | 254 (12.9) | | |
| N stage\textsuperscript{a} | | | | |
| N0 | 48 (88.9) | 1550 (81.0) | 0/104 | 0.114 |
| N1 | 1 (1.9) | 120 (6.3) | | |
| N2 | 5 (9.3) | 219 (11.4) | | |
| N3 | 1 (2.6) | 25 (1.3) | | |
| M stage (yes)\textsuperscript{a} | 0 (0.0) | 23 (1.2) | 2.153 | 0.673 |
| TNM—stadium\textsuperscript{a} | | | | |
| Stadium I | 22 (44.0) | 635 (36.0) | 5/254 | 0.210 |
| Stadium II | 16 (32.0) | 467 (26.5) | | |
| Stadium III | 3 (6.0) | 264 (15.0) | | |
| Stadium IV | 9 (18.0) | 398 (22.6) | | |
| Treatment, No. (%) | | | | |
| Surgery (yes) | 16 (29.1) | 467 (23.1) | 0/0 | 0.303 |
| Chemotherapy (yes) | 1 (1.8) | 45 (2.2) | 0/0 | 0.838 |
| Radiotherapy (yes) | 46 (83.6) | 1699 (84.2) | 0/0 | 0.911 |
| Previous malignancy (yes), No. (%) | 12 (22.6) | 299 (14.8) | 2/0 | 0.120 |

Cases: IBD patients with larynx carcinoma; controls: patients in the general population with larynx carcinoma derived from the NCR.

Abbreviation: SCC, squamous cell carcinoma.

\textsuperscript{a}According to the 7th TNM edition.

IBD patients (14% vs 0.5%; \( P < 0.01)\textsuperscript{38} It could be speculated that the phenotype of elderly-onset IBD is associated with a higher risk of cancer.\textsuperscript{28, 39} On the other hand, the high prevalence of tobacco use in LC patients may result in late UC onset and confound our findings. Indeed, we found tobacco use to be an independent risk factor for LC development, especially in CD patients (data lacking for UC). This is consistent with the current literature about risk factors for LC.\textsuperscript{40} Although stricturing disease and penetrating disease in CD patients were independent risk factors for LC development regardless of tobacco use, tobacco use may contribute to ongoing inflammation and result in stricturing and penetrating disease.

To our knowledge, this is the largest systematically collected series of data from LC patients with IBD, which is the major strength of this study. Nonetheless, there are some limitations of our study that need to be addressed. First, the retrospective design resulted in missing data. For example, data regarding the exact time period of immunosuppressive...
FIGURE 3. A, Laryngeal carcinoma survival curves. B, Laryngeal carcinoma survival curves after adjusting for TNM stage. *Confounder correction, including TNM stage.
medication use were lacking, impeding analysis of the impact of immunosuppressive medication on LC development. Moreover, the date of IBD diagnosis may be not completely reliable, as this was extracted from the PALGA database. Second, we used 3 different databases to collect all data, as there was not 1 database that contained all required data. Data from the IBDSL and NCR were collected prospectively, whereas data from our cases were collected retrospectively. Finally, the use of preconceived databases may result in missing parameters. As such, data on alcohol use are lacking.

In conclusion, we found no difference in survival between IBD patients with LC and the general LC population. Moreover, immunosuppressive medication did not impact survival. Male sex was an independent risk factor for LC development in IBD patients. Elderly-onset IBD emerged as a risk factor for LC development, particularly in UC patients. Smoking and strictureing or penetrating disease were independent risk factors in CD patients for the development of LC. Based on our results, routine screening for LC is discouraged in IBD patients, as the LC incidence is low.

REFERENCES
1. Eaden JA, Abrams KR, Mayberry JF. The risk of colorectal cancer in ulcerative colitis: a meta-analysis. Gut. 2001;48:526–535.
2. Rutter M, Saunders B, Wilkinson K, et al. Severity of inflammation is a risk factor for colorectal neoplasia in ulcerative colitis. Gastroenterology. 2004;126:451–459.
3. Biancone L, Onali S, Petruzziello C, et al. Cancer and immunomodulators in inflammatory bowel diseases. Inflamm Bowel Dis. 2015;21:674–698.
4. Beaumer L. Inflammatory bowel disease therapies and cancer risk: where are we and where are we going? Gut. 2012;61:476–483.
5. Pedersen N, Duricova D, Elkjaer M, et al. Incidence of colorectal cancer in inflammatory bowel disease: meta-analysis of population-based cohort studies. Am J Gastroenterol. 2010;105:1480–1487.
6. Beaumer L, Sokol H, Seki P. Noncolorectal malignancies in inflammatory bowel disease: more than meets the eye. Dig Dis. 2009;27:375–381.
7. Giagkou E, Saridi M, Albani E, et al. Dermal lesions and skin cancer in patients with inflammatory bowel disease receiving immunosuppressive therapy. Asian Pac J Cancer Prev. 2018;19:2845–2851.
8. Lemaître M, Kirchgesner J, Rudnichi A, et al. Association between use of thiopurines or tumor necrosis factor antagonists alone or in combination and risk of lymphoma in patients with inflammatory bowel disease. JAMA. 2017;318:1679–1686.
9. Kinen L. Incidence of cancer in rheumatoid arthritis and other disorders after immunosuppressive treatment. Am J Med. 1985;78:44–49.
10. Gutierrez-Dalman A, Campistol JM. Immunosuppressive therapy and malignancy in organ transplant recipients: a systematic review. Drugs. 2007;67:1167–1198.
11. Preciado DA, Matas A, Adams GL. Squamous cell carcinoma of the head and neck in solid organ transplant recipients. Head Neck. 2002;24:319–325.
12. Dalainis T. Human papillomavirus and oropharyngeal cancer, the epidemics, and significance of additional clinical biomarkers for prediction of response to therapy. Int J Oncol. 2014;44:1799–1805.
13. Omere Celebi O, Sener E, Hosal S, et al. Human papillomavirus infection in patients with laryngeal carcinoma. BMC Cancer. 2018;18:1005.
14. Liu ZN, Wang WT, Yan LN, Liver Surgery Group. De novo malignancies after liver transplantation with 14 cases at a single center. Transplant Proc. 2015;47:2483–2487.
15. Nure E, Frongillo E, Lirosi MC, et al. Incidence of upper aerodigestive tract cancer after liver transplantation for alcoholic cirrhosis: a 10-year experience in an Italian center. Transplant Proc. 2013;45:2733–2735.
16. Marques Medina E, Jimenez Romero C, Gomez de la Cámara A, et al. Malignancy after liver transplantation: cumulative risk for development. Transplant Proc. 2009;41:2447–2449.
17. Adam J, Gobel H, Lindelof B, et al. Cancer risk following organ transplantation: a nationwide cohort study in Sweden. Br J Cancer. 2003;89:1221–1227.
18. Bonetta A, Bandera L, Roviello G, et al. Neoadjuvant chemotherapy and radical radiotherapy associated with cetuximab for laryngeal cancer in a pancreas and renal recipient. Anticancer Drugs. 2016;27:470–473.
19. Shimohara ET, Maita A, Jha N, et al. Sirolimus as a potential radiosensitizer in squamous cell cancer of the head and neck. Head Neck. 2009;31:406–411.
20. Vilas-Boas F, Magro F, Balhau R, et al. Oral squamous cell carcinoma in a Crohn’s disease patient taking azathioprine: case report and review of the literature. J Crohns Colitis. 2012;6:792–795.
21. Li AC, Warnakulasuriya S, Thompson RP. Neoplasia of the tongue in a patient with Crohn’s disease treated with azathioprine: case report. Eur J Gastroenterol Hepatol. 2003;15:185–187.
22. Giagkou E, Christodoulou DK, Katsanos KH. Mouth cancer in inflammatory bowel diseases. Oral Dis. 2016;22:260–264.
23. Nissen LHC, Derick LAAP, Jacobs AME, et al. Dutch Initiative on Crohn and Colitis (ICC); Dutch Head and Neck Society; PALGA Group; IBD/NHC Group. Risk factors and clinical outcomes of head and neck cancer in inflammatory bowel disease: a nationwide cohort study. Inflamm Bowel Dis. 2018;24:2015–2026.
24. Biancone L, Orlando A, Kohn A, et al. Infliximab and newly diagnosed neoplasia in Crohn’s disease: a multicentre matched pair study. Gut. 2006;55:228–233.
25. Casparie M, Tiebosch AT, Burger G, et al. Pathology databanking and biobanking in the Netherlands, a central role for PALGA, the nationwide histopathology and cytopathology data network and archive. Cell Oncol. 2007;29:19–24.
26. van den Heuvel TR, Jonkers DM, Jeuring SF, et al. Cohort profile: the Inflammatory Bowel Disease South Limburg Cohort (IBDSL). Int J Epidemiol. 2017;46:e7.
27. Nissen LHC, Pierik M, Deriks LAAP, et al. Risk factors and clinical outcomes in patients with IBD with melanoma. Inflamm Bowel Dis. 2017;23:2018–2026.
28. Nissen LH, Assendorp EL, van der Post RS, et al. Impaired gastric cancer survival in patients with inflammatory bowel disease. J Gastrointestin Liver Dis. 2016;25:431–440.
29. Watanabe T, Konishi T, Kishimoto J, et al; Japanese Society for Cancer of the Colon and Rectum. Ulcerative colitis-associated colorectal cancer shows a poorer survival than sporadic colorectal cancer: a nationwide Japanese study. Inflamm Bowel Dis. 2011;17:802–808.
30. Penn I. Post-transplant malignancy: the role of immunosuppression. Drug Saf. 2000;23:101–113.
31. Jharp B, Seinen ML, de Boer NK, et al. Thiopurine therapy in inflammatory bowel disease patients: analyses of two 8-year intercept cohorts. Inflamm Bowel Dis. 2010;16:1541–1549.
32. Annese V, Beaugerie L, Egan L, et al; EECO. European evidence-based consensus: inflammatory bowel disease and malignancies. J Crohns Colitis. 2015;9:945–965.
33. Baars JE, Kuipers EJ, van Haastert M, et al. Age at diagnosis of inflammatory bowel disease influences early development of colorectal cancer in inflammatory bowel disease patients: a nationwide, long-term survey. J Gastroenterol. 2012;47:1308–1322.
34. Brackmann S, Andersen SN, Aamodt G, et al. Two distinct groups of colorectal cancer in inflammatory bowel disease. Inflamm Bowel Dis. 2009;15:9–16.
35. Derick LA, Nissen LH, Drenth JP, et al; Dutch Initiative on Crohn and Colitis; PALGA Group; IBD/NHC Group. Better survival of renal cell carcinoma in patients with inflammatory bowel disease. Oncotarget. 2015;6:38336–38347.
36. Kishikawa J, Hata K, Kazama S, et al. Results of a 36-year surveillance program for ulcerative colitis-associated neoplasia in the Japanese population. Dig Endosc. 2018;30:236–244.
37. Butter M, Weiler S, Biedermann L, et al. Clinical manifestations, pathophysiology, treatment and outcome of inflammatory bowel diseases in older people. Maturitas. 2018;110:71–78.
38. Mafonia M, Calafat M, de Francisco R, et al; GETECCU. Phenotype and natural history of elderly onset inflammatory bowel disease: a multicentre, case-control study. Aliment Pharmacol Ther. 2018;47:605–614.
39. Charpentier C, Salleron J, Savoye G, et al. Natural history of elderly-onset inflammatory bowel disease: a population-based cohort study. Gut. 2014;63:423–432.
40. Hashibe M, Brennan P, Chuang SC, et al. Interaction between tobacco and alcohol use and the risk of head and neck cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. Cancer Epidemiol Biomarkers Prev. 2009;18:541–550.