Review Article

Oral Cancer and Oral Precancerous Lesions in Inflammatory Bowel Diseases: A Systematic Review

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Abstract

Oral cancer is historically linked to well-known behavioural risk factors such as tobacco smoking and alcohol consumption. Other risk factors include age over 40, male sex, several dietary factors, nutritional deficiencies, viruses, sexually transmitted infections, human papillomavirus, chronic irritation, and possibly genetic predisposition. Precancerous lesions in the oral cavity include leukoplakia, erythroplakia, and lichen planus. Histology of oral cancer varies widely but the great majority are squamous cell carcinomas.

Epidemiological studies and cancer registries have shown a consistently increased risk of oral malignancies in kidney, bone marrow, heart, or liver transplantation, in graft vs host disease, and in patients with HIV infection. Because of the increasing use of immunosuppressive drugs in patients with inflammatory bowel disease, it is useful to more accurately delineate the consequences of chronic immunosuppression to the oral cavity. Oral cancer and precancerous oral lesions in patients with inflammatory bowel disease [IBD] have been scarcely reported and reviews on the topic are lacking.

We conducted a literature search using the terms and variants of all cancerous and precancerous oral manifestations of inflammatory bowel diseases. By retrieving the existing literature, it is evident that patients with IBD belong to the high-risk group of developing these lesions, a phenomenon amplified by the increasing HPV prevalence. Education on modifiable risk behaviours in patients with oral cancer is the cornerstone of prevention.

Oral screening should be performed for all IBD patients, especially those who are about to start an immunosuppressant or biological drug.

Keywords: Inflammatory bowel disease; Crohn's disease; ulcerative colitis; oral cancer; oral malignancy; oral precancerous lesions; immunosuppressant; azathioprine; biological therapies; anti-TNF-α.

1. Introduction

Epidemiological studies and cancer registries have shown a consistently increased risk of head and neck malignancies in patients undergoing kidney, bone marrow, heart or liver transplantation, in graft vs host disease, and in patients with HIV infection, although the calculated risk differs markedly between studies essentially because of differences in methodologies and selection of patients.
Skin, lip, buccal cavity, and tongue cancers, lymphomas, melanomas, and Kaposi’s sarcomas, are the main types of cancer reported in these patients.\(^1\)

Oral cancer is historically linked to well-known behavioural risk factors such as tobacco smoking and alcohol consumption. Other main risk factors are age over 40 and male sex.\(^2\) In addition, several dietary factors, nutritional deficiencies, viruses, sexually transmitted infections, chronic irritation, and possibly genetic predisposition have been associated with oral cancer.\(^3\)

Substantial evidence has been mounting that human papillomavirus [HPV] infection is playing an increasing important role in oral cancer. In fact, HPV infection is recognized as one of the major causes of infection-related cancer worldwide. Indeed, strong evidence for a causal aetiology with HPV has been reported by the International Agency for Research on Cancer for cancers of the cervix, penis, vulva, vagina, anus, and oropharynx including base of the tongue and tonsils. Of the estimated new cancers occurring each year worldwide, 4.8% are attributable to HPV infection, with substantially higher incidence and mortality rates seen in developing vs developed countries.\(^4\)

Extra-intestinal malignancies in inflammatory bowel disease [IBD] have been linked with various aetiologies except IBD itself. Oral cancer and precancerous oral lesions in patients with IBD have been scarcely reported and reviews assessing the magnitude of this problem are lacking.

Herein, we review systematically all data on epidemiology, aetio-pathogenesis, and risk factors of oral malignant and pre-malignant lesions and conditions associated with IBD, and we provide a comprehensive guide for clinicians regarding the principles of optimal therapeutic management of these challenging extra-intestinal malignancies in patients with IBD.

2. Search strategy
A comprehensive literature search using the terms and variants of all cancerous and precancerous oral manifestations of inflammatory bowel diseases [ulcerative colitis, Crohn’s disease] was performed in January 2015 within Pubmed, Embase, and Scopus and was restricted to human studies [1946 to January, 2015] and EMBASE [1947 to January, 2015]. Studies were included if they were published in any language and if related to oral malignant or pre-malignant lesions or conditions with special focus on IBD. Additionally, references from relevant literature were hand-searched [search strategy is available in the Appendix in Supplementary Data at JCC online].

3. Epidemiology and pathogenesis of oral cancer
The term oral cancer refers to cancers of the mucosal surfaces of the lips, floor of mouth, tongue, buccal mucosa, lower and upper gingival surfaces, hard palate, and retromolar trigone.\(^5\)

Head and neck cancer represent the sixth most common malignancy worldwide and the annual incidence of oral cancer exceeds 300 000 new cases.

Several aetiopathogenetic mechanisms have been suggested so far [Figure 1] but the pathogenesis of oral cancer still needs further elucidation. There are several reports on mucosal immunodeficiency in smokers and on changes of the saliva in patients under immunosuppressive or anti-neoplastic therapy.\(^6\) Reduced saliva volume and change in saliva constituents may affect epithelial maintenance and repair, the physiology of the oral microflora, and the interaction between the oral flora and the epithelium.\(^7\) Chronic oral candidiasis has been also suggested as a potential pathogenetic mechanism especially in patients with prolonged steroid use.\(^8\)

4. Risk factors of oral cancer
Risk factors for oral cancer can be divided into precancerous lesions and precancerous states such as conditions related to lifestyle [ie smoking, alcohol consumption], to medical therapy, or to carriage of oncogenic viruses.

4.1. Precancerous lesions
Diagnosis of oral cancerous lesions is generally easy but early recognition of precancerous lesions and precancerous conditions is often challenging, especially in patients that belong to high risk groups. It is important to underline here that most oral cancers do not develop from pre-existing precancerous lesions.

Precancerous lesions include chronic lesions of the oral cavity among which cancer of the oral cavity is known to develop with low to high probability.\(^9\) These lesions include: leukoplakia, oral lichen planus, erythroplakia, papillomatous lesions, actinic cheilitis, submucosal fibrosis, keratotic candidiosis, and tertiary syphilis. The precancerous states include cancers occasionally observed in the oral cavity during any kind of immunosuppression or other conditions related to therapy and to lifestyle.\(^10\)

4.1.1. Oral lichen planus
Oral lichen planus is a common disease of unknown aetiology affecting oral mucosa. It is characterised by T cell–mediated chronic inflammation and has been clinically associated with development of oral squamous cell carcinoma, although the risk for neoplastic change seems low [Figure 2].\(^11\) Malignant transformation is seen in less than 2% of the patients within 10–15 years.\(^12\)

Histologically oral lichen planus does not differ from the oral lichenoid reactions which are lesions mostly found in contact with amalgam restorations. In such cases, a causative treatment with replacement of the amalgam is recommended.

4.1.2. Leukoplakia, erythroplakia, and erythroleukoplakia
The most frequent causes of leukoplakia and erythroplakia are smoking, chewing tobacco, and poorly fitting dentures. Most cases of leukoplakia do not develop into cancer, but some leukoplakias are either cancerous when first found or have precancerous changes. Erythroplakia and erythroleukoplakia are less common but are usually more serious.\(^13\)

Oral hairy leukoplakia has been suggested as a marker for severe immunosuppression and was initially described in immunocompromised men infected with the human immunodeficiency virus [HIV] but has also been described in other iatrogenic instances such as in immunocompromised and transplanted patients.

4.2. Precancerous states
4.2.1. The role of immunosuppression
Immunosuppressive drugs seem to substantially contribute to skin/lip and oral cancer development after organ transplantation, either as a result of immunosuppression or through specific carcinogenic mechanisms [Appendix Table 1, available as Supplementary data at JCC online]. Prolonged immunosuppression for multiorgan chronic graft-vs-host disease increases the risk of oral cancer\(^14\) and double or triple immunosuppression also increases this risk.\(^15\) In addition, the
extent of immunosuppression as expressed by lower total leukocyte count was related to an increased risk of hairy leukoplakia in kidney transplant patients.19

### 4.3. Thiopurines

Thiopurines [azathioprine, 6-mercaptopurine, and 6-thioguanine] may promote cancers by various mechanisms including carcinogenic mutations of cell DNA, impaired immunosurveillance of tumour cells, impaired number or function of immune cells chronically infected by Epstein-Barr Virus [EBV] or HPV, and several others.

#### 4.3.1. Methotrexate

In general, the use of methotrexate [MTX] monotherapy or in combination with other immunosuppressants has been reported to be safe in rheumatology20 or in patients with psoriasis.21 Of note, MTX has been used as anti-neoplastic therapy for head-neck cancers and for oral florid papillomatosis.22

#### 4.3.2. Corticosteroids

A single study suggested that the use of oral glucocorticoids may increase the risk of skin cancers, in particular, among patients other than organ transplant recipients, but this has to be further confirmed.23

### 4.3.3. Biological therapies

Tumour necrosis factor-alpha [TNF-α] is a cytokine produced by activated T cells and macrophages determining in vitro a necrotising effect on tumour cells. Blocking TNF-α has therefore been hypothesised to increase the overall cancer risk.

Rare cases of oral cancer or precancerous lesions following anti-TNF-α and biological therapies have been reported in non-IBD patients [Appendix Table 2, available as Supplementary data at JCC online], including also one case of oral candidiasis in a patient with sarcoidosis on infliximab.24 Another study on the influence of TNF-α blockers on the oral prevalence of opportunistic microorganisms in patients with ankylosing spondylitis showed that anti-TNF-α therapy could not be correlated with increased counts of microorganisms.25

Studies including patients with rheumatoid arthritis on anti-TNF α therapies did not find any evidence for an excess cancer risk on TNF-α antagonists but, according to the authors, an excess cancer risk after several years of exposure cannot be ruled out.26

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**Figure 1.** The puzzle of mechanisms and conditions leading to the development of oral precancerous lesions and oral cancer in inflammatory bowel diseases.
The past few years have seen an increased interest in the implications of integrin receptors in cancer biology and tumour cell aggression. No case of oral cancer during anti-integrin therapy has been so far reported. Long-term risk assessment of oral cancer in patients on biological requires observational studies and safety assessments using randomised controlled trials meta-analyses.

4.4. Oncogenic viruses

4.4.1. Human papillomavirus [HPV]

A rise in incidence of oropharyngeal squamous cell cancer in non-transplanted White men younger than 50 years, who have no history of alcohol or tobacco use, has been recorded over the past decade and this was associated with human papillomavirus [HPV-16] infection. Of interest, the biology of HPV-positive oropharyngeal cancer is distinct, with P53 degradation, retinoblastoma RB pathway inactivation, and P16 upregulation. By contrast, tobacco-related oropharyngeal cancer is characterised by TP53 mutation. Sometimes the term ‘oropharynx’ introduces a confusion as, according to some physicians, it is meant to include also the buccal cavity. In fact, the oropharynx includes everything that lies behind the tonsils. So on the one hand it is right to support that oropharyngeal cancers are linked to HPV but, on the other hand, in the buccal cavity, the role of HPV is debatable. Thus a clear separation for the role of HPV regarding carcinogenesis in the buccal cavity and the oropharynx has to be evaluated.

4.4.2. Epstein-Barr virus [EBV]

Epstein-Barr virus [EBV] is classically associated with Burkitt’s lymphoma, B-cell lymphoproliferative syndromes, nasopharyngeal carcinoma, Hodgkin disease, T-cell lymphomas, thymic lymphoepithelial carcinoma, gastric carcinoma, and oral hairy leukoplakia. EBV presence and oral manifestations have been also reported in patients who had undergone bone marrow transplantation and heart transplantation.

5. Taxonomy of oral cancerous lesions

Taxonomy of oral cancerous lesions includes location, histology, and HPV positivity.

5.1. Taxonomy by location

5.1.1. Lip cancer

A case of squamous cell carcinoma of the lip associated with adalimumab therapy for ankylosing spondylitis has been reported so far. Although the increased risk of non-melanoma skin cancer, including dysplastic and malignant lip lesions, in immunosuppressed solid organ transplant patients is well known, the association with inflammatory bowel disease remains unknown.

5.1.2. Buccal cancer

Among the most common malignancies observed in transplant recipients were non-melanomatous skin cancers and squamous cell cancers of the buccal cavity.

5.1.3. Gingival cancer

Gingival cancer can be primary or metastatic. The most common primary sources of metastatic tumours to the oral region are the breast, lung, kidney, bone, and colon; choriocarcinoma and hepatocellular carcinoma metastatic to the maxillary gingival area may also occur.
5.1.4. Tongue cancer
In transplant recipients, erythroplakia of the tongue, lymphoproliferative disease, and squamous cell tongue carcinoma have been described.

5.2. Taxonomy by histology and HPV positivity
Histology of oral cancer varies largely but more than 9 of 10 cancers of the oral cavity and oropharynx are squamous cell carcinomas [Figure 3]. There are also other types, including non-squamous, lymphoma, melanoma [Figure 4], non-melanoma, metastatic, and other rare types such as Kaposi sarcomas [Figure 5]. Finally, characterisation of oral cancers by HPV positivity is important for disease diagnosis and prognosis.

6. Oral cancer prognosis
Prognosis of oral cancer differs significantly among specific oral locations, with cancer of the lip, for example, having a much better prognosis compared with a cancer at the base of tongue or on the gingiva. Prognosis of intra-oral cancer is generally poor, with a 5-year survival less than 50%. Especially in post-transplant oral tumours, outcomes are worse compared with the normal population. Local recurrences occur in a significant percentage of patients, whereas distant metastases are less frequent. Prognosis correlates mainly with the size of the lesion and the nodal status at the time of diagnosis. Of importance, HPV positivity is correlated with better cancer outcomes. A significant association of p16 [INK4a] overexpression with improved survival in young patients with squamous cell cancers of the oral tongue has also been demonstrated. However, p16 [INK4a] overexpression was not a reliable predictor of HPV positivity.

7. Epidemiology of oral cancer in IBD
The incidence and prevalence of oral cancerous and pre-cancerous lesions in IBD is currently unknown. It could also be possible that oral cancers in IBD were grouped together in the past within the upper digestive track cancers or head and neck cancers group, thus overshadowing the exact magnitude of the problem. Moreover, no routine oral screening for IBD patients, including those who are about to start an immunosuppressant or a biological therapy, is performed or is advised so far.

Direct or indirect information on the occurrence of oral malignancies in IBD was extracted—with every possible caution and after meticulous search and analysis—from large cohort studies, clinical trials, and rare case reports [Table 1]. According to these data, the prevalence of oral cancer in IBD seems probably to be low, as the risk for oral cancer in IBD has been estimated to range (risk ratio [95% confidence interval]) from 1.08 [0.31–3.70] to 1.78 [0.37–5.21].

Taking into account all above limitations in the oral cancer risk calculations, it is evident that well-designed prospective studies are urgently needed to clearly assess the real magnitude of the risk of oral cancer in IBD and to possibly identify high-risk groups of patients needing close surveillance.

8. Risk factors of oral cancer in IBD
8.1. Precancerous lesions
Although the prevalence of these lesions has been reported to be significantly increased in transplant recipients, they have been rarely reported in patients with IBD [Table 2]. Successful adalimumab use for oral lichen planus has been reported and there are also reports on paradoxical triggering of erosive lichen planus during infliximab treatment and of de novo oral lichen planus occurrence after certolizumab pegol treatment in a patient with Crohn’s disease. Oral hairy leukoplakia has been once reported in a patient with ulcerative colitis. Of note, precancerous lesions have to be distinguished from precancerous states.

8.2. Treatment-related risk factors
IBD patients receiving immunosuppressive therapy are theoretically at an increased risk of developing extra-intestinal malignancies.
However, the exact magnitude of this risk is currently unknown as it may occur in cancers where absolute numbers may be low but relative risk may be high.

8.2.1. Thiopurines
So far, two cases of oral cancer during azathioprine [AZA] therapy have been reported in IBD, both in patients with Crohn’s disease. The first was a case of a 39-year-old non-smoking male with Crohn’s disease who had been treated for 3 years with azathioprine and developed a lingual ulcer. Biopsy revealed squamous cell carcinoma of the tongue. The second one was a case of a 33-year-old Caucasian woman with Crohn’s disease treated with azathioprine for 9 years, who developed an ulcerated lesion at the right superior retromolar trigone and in which subsequent biopsy revealed a squamous cell carcinoma.

In general, in patients with IBD, azathioprine use was associated with an increased risk of overall cancer [rate ratio = 1.41, 95% confidence interval: 1.15, 1.74], whereas former use of azathioprine [rate ratio = 1.02, 95% confidence interval: 0.83, 1.25] or increasing cumulative received doses were not. Patients with IBD with a history of cancer are at increased risk of developing any new or recurrent cancer, with a predominant incidence of new cancers. Treatment with immunosuppressants has no overall major impact per se on this risk.

It should be emphasised that the doses of immunosuppression used in transplanted patients are significantly higher than those used in IBD, so it is difficult to suggest a parallel degree of risk.

8.2.2. Methotrexate
No case of oral cancer during methotrexate [MTX] therapy for IBD has been reported so far. In addition, there is no study in the literature supporting an excess risk of cancer in IBD patients who are exposed to methotrexate.

8.2.3. Calcineurin inhibitors
Cyclosporin A and tacrolimus are used in a minority of patients with IBD and most of the time on a short-term basis. No safety data are available on the risks of cancer associated with the use of these drugs in IBD and no case of oral cancer has been so far reported during or after the use of these two drugs.

8.2.4. Corticosteroids
There is no report on oral cancer following corticosteroid use in IBD patients so far.

8.2.5. Biological therapies
Several studies have investigated the cancer risk associated with anti-TNF use in IBD but none of them has focused on oral cancer risk. One limitation of these studies is that most of the IBD patients treated with anti-TNFs have either a concurrent or a past use of thiopurines, thus making difficult to evaluate the cancer risk related to anti-TNFs alone. Current evidence suggests that the use of anti-TNFs alone in IBD is not associated with a significant increase in the overall cancer risk. There are also scarce reports on oral cancer during biological therapy in other autoimmune-based diseases.

No case of oral cancer during anti-integrin therapy in IBD has been reported so far.

9. Treatment of oral cancer in IBD patients

9.1. Conventional treatment of oral cancer
Conventional treatment approaches of oral cancer include surgery, radiotherapy, and adjuvant systemic chemotherapy. Various combinations of these approaches may be selected depending on the disease presentation and pathological findings. Treatment of oral precancerous lesions includes surgical excision or topical application of calcineurin inhibitors, but therapy has to be individualised.

9.2. Modification of immunosuppression
Management of immunosuppression in patients with IBD diagnosed also with oral cancer or precancerous lesions is challenging. Modification of immunosuppression has been proved to be important in those patients, but the detailed principles of management of immunosuppression after cancer diagnosis are debatable.
Changing the immunosuppressive regimen from azathioprine to cyclosporin or vice versa does not seem to relieve skin predisposition to cancer. Apart from immunosuppressive therapy modifications, exposure to sunlight and infection with human papillomaviruses, as well as oral screening for pre-existent occult carcinomas, are believed to represent the most important preventive measures.
9.3. Special oncological issues and prevention of recurrence

Primary or metastatic tumours to the oral region have to be always excluded before starting immunomodulators or biological therapies in IBD patients. In cases with documented oral precancerous lesions, the prioritisation of treatment has to be set on an individual basis.

Oral surveillance strategies in patients exposed to immunosuppressants and biologicals is mandatory before initiation and during any therapy. Annual examination by a dermatologist, a stomatologist, and an ear-nose-and-throat oncologist specialist is mandatory in those patients. Based on the examination of specialists, risk assessment according to the individual risk factors [i.e., smoking, precancerous lesions] and tailored case-by-case surveillance strategy defined for each patient will be performed.66

Management decisions regarding immunosuppression in IBD patients with a cancer are best made in a multidisciplinary fashion and on a case-by-case basis, taking into account the natural history of the cancer (organ of origin, stage, histological type, and prognosis). This should include the opinion of the oncologist, the time from completion of cancer treatment, the severity of the IBD, and the expected impact of the immunosuppressants on the previous cancer. It seems reasonable to withhold immunosuppressants during the treatment of active oral cancer.

Within 2 years after completing cancer treatment, 5-aminosalicylates, corticosteroids, antibiotics, nutritional therapy, and surgery should form the foundation of IBD treatment. However, if these treatment modalities are ineffective in a patient with severe IBD, then immunosuppressive therapy should be considered as rescue therapy. If a tumour has an intermediate to high risk of recurrence, an interval of 5 years is preferable. In all cases, if immunosuppressive therapy is resumed, a step-up approach should be considered, starting with monotherapies.

Anti-TNF therapy is contraindicated in patients with a history of lymphoma and careful consideration should be given to initiating anti-TNF therapy in those with a history of oral cancer.67 The use of anti-TNF therapies in IBD patients with previous oral malignancy remains a challenging topic to address because, in general, patients with previous oral malignancy are not likely to be prescribed a TNF inhibitor at least on a short-term follow up.70

Although there are few data regarding the impact of steroids on cancer, the general consensus is that corticosteroids are the safer option, although anti-TNFs may be a useful back-up plan.

Overall, the risks associated with biological agents should be weighed against their potential benefits in patients with previous oral malignancy as should be done in any patient. Education on modifiable risk behaviours in patients with oral cancer is the cornerstone of prevention. HPV vaccination, oral hygiene practices, and annual dental screening starting from the early childhood are mandatory.71

Oral lesions can be easily observed by direct visualisation; however, proper training and knowledge of the differential diagnosis of oral lesions is mandatory for early diagnosis of malignant and premalignant lesions in the oral cavity. In selected cases, image analysis of tongue smears is important. Finally, standardised surveillance policies have to be implemented in high-risk groups.72

10. Conclusions

Oral cancerous and precancerous lesions have been reported in patients with IBD as they have already been reported for years now in other groups of immunosuppressed or transplanted patients. By retrieving the existing literature, it became evident that patients with IBD belong to the high-risk group of developing these lesions, a phenomenon amplified by the increasing HPV prevalence. Currently no special precautions have been implemented to modify this risk and there are no standard approaches or guidelines for the optimal screening and disease management in such complex cases. We need prospective studies to assess the prevalence, risk, and prognosis of oral cancer in well-defined IBD patient groups.

It would be of importance to implement strategies for better physician and patient awareness regarding this important topic, particularly in the view of the new and evolving therapies for inflammatory bowel diseases.

Conflict of Interest

None declared.

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Supplementary Data

Supplementary data to this article can be found at ECCO-JCC online.

References

Oral Cancer and IBD


