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Candida Quantification and Species identification in Patients undergoing Postoperative Head and Neck Radiotherapy and Combination of Chemo-Radio Therapy

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ABSTRACT

Introduction: Candidiasis is found to occur frequently in patients undergoing Radiotherapy and Chemotherapy alone or in combination. Mucositis is another common finding post cancer therapy in head and neck region. Hence this study was undertaken to evaluate and compare candidial quantification and species identification in patients prior to post-operative radiotherapy(PORT) and in fourth week of PORT and among combination of Radiotherapy and Chemotherapy (CTRT) groups in Indian population and gradation of mucositis and also to determine sensitivity profiles of candida species.
Materials and methods- 40 patients who had undergone operative procedure for head and neck cancer were divided into 2 groups - Group 1 radiation therapy (RT) and Group 2 chemotherapy and radiotherapy (CTRT). Microbiological evaluation of candida colonization was carried out prior to radiation and in the fourth week of radiotherapy using the oral rinse method. Species identification helped in determining the sensitivity profiles to various antifungal drugs.
Results- Candida albicans along with non albicans species like C. tropicalis,C. krusie, C.glabrata and C.parapsilosis were identified. Among the non albicans species, C tropicalis was the most common. Mixed species were detected in multiple samples. Grade 2 mucositis was predominant in both treatment modalities. Treatment interruptions occurred due to systemic complications in our patients. When albicans and non albicans group were compared, C albicans was 100% sensitive to all the antifungal drugs tested except fluconazole. All other organisms were 100% sensitive to voriconazole, capsofungin and itraconazole.
Conclusion- Candida albicans was the most common species present and C tropicalis was the most common non albicans fungal organism. Sensitivity revealed that voriconazole, capsofungin and itraconazole can be considered for antifungal prophylaxis during radiotherapy and chemotherapy of head and neck cancers.

Keywords
Cancer therapy, Candida species, chemotherapy, fungal sensitivity, mucositis, radiotherapy

Introduction

Head and neck cancers are among the ten most common cancers accounting for more than 550,000 cases annually worldwide.[1] In India, it accounts for 1/4th of cancers in males and 1/10th of cancers in females.[2] The common modalities of treatment of head and neck cancers involve either surgery, radiation and chemotherapy administered alone or in combination. Most patients with head and neck cancer radiotherapy develop notable mucositis and oral candidiasis as an adverse effect.

The role of post operative chemoradiotherapy (CTRT) for head and neck cancers has been established by the landmark studies conducted by Radiation Treatment and Oncology Group (RTOG) and European Organization of Research and Treatment of Cancer (EORTC).[3,4] Although there are studies on the incidence of candidiasis following primary chemoradiation for head and neck cancers, very little studies were done regarding the species identification of Candida in the post-operative chemotherapy setting.

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Mucositis along with candidal infection has been found to affect the oral cavity of patients who had undergone chemotherapy and radiotherapy. In order to administer effective treatment species identification of Candida is essential. WHO has graded mucositis according to their severity (WHO grading)[5]. The sensitivity of various candida species to different antifungal drugs has to be assessed so that an appropriate drug could be administered as prophylactic measure to reduce patient discomfort during post-operative radiotherapy(PORT) and chemotherapy. Hence this study was undertaken to evaluate the Candidal infection in the oral cavity before and after fourth week of treatment among patients undergoing radiotherapy after surgery- Post Operative Radio Therapy(PORT) alone and to compare them with those of patients undergoing both chemotherapy(CT) and in Radiotherapy (CTRT). The secondary objective of the study was to analyse the antibiotic sensitivity to the different Candidal species identified.

Methods

The study group included 40 patients, sourced from the department of Radiation Oncology, Amrita Institute of Medical Sciences. Informed consent and ethical committee clearance were obtained prior to the beginning of the study. All patients had undergone an operative procedure as part of the management protocol for cancer. The patients were divided into 2 groups, Group 1 comprised of RT patients and Group 2 comprised of CTRT patients.

Inclusion criteria were only patients between 25 and 70 years of age and Head and neck cancer patients planned for either post-operative radiotherapy or CTRT. Patients receiving a total radiation dose of 6000-7000cGy (200fractions/day)and patients receiving weekly chemotherapy of cisplatin(50mg) were selected.

Patients withuncontrolled diabetes mellitus, previously irradiated patients, presence of oral lesions such as stomatitis, ulcer and patients using dentures were excluded.

All patients were examined in the dental clinic. Comprehensive oral health care was administered. Clinical intra- oral photographs of buccal mucosa and palate prior to PORT, CTRT and during the fourth week of treatment were recorded to visually assess the mucosal changes. Mucositis was graded according to WHO classification.[5]

Microbiological evaluation of candidal colonization were carried out prior to radiation and in the fourth week of radiotherapy. On each visit, the samples were collected using the oral rinse method[6] where patients were asked to rinse their mouth for 60 seconds with 10 ml of saline and expectorated into a universal container and immediately transported for microbiological evaluation. This procedure was repeated in the 4^{th} week also.

Candida isolates was identified by detection of color characteristic on CHROM Agar candida plates and confirmed by VITEK-2. Antifungal sensitivity was done using VITEK-Compact-C ID 32C. (Biomerieux, France). Chi-square was used for statistical analysis using SPSS version 14. A p value of 0.05 was taken as the level of significance.

Results

In the RT group, the prevalence of Candida albicans species were found in 45.4% of the patients both prior to and in the 4^{th} week of Radiotherapy. The non-albicans species of C. krusei and C. sacharavesie were seen in 9.09% of the patients both prior to and in the 4^{th} week of radiotherapy. C. glabrata was found in 9.09% of the patients prior to RT, and none was seen in the 4^{th} week of RT. While C.tropicalis , C. parapsilosis and T. asahii were not identified in patients prior to PORT, the three species were found to be 9.09% among patients in the 4^{th} week of PORT.

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(Table1) Non-albicans group increased from 27.27% of the patients identified as having Candidal infection to 45.4% in samples taken prior and during the RT.
On comparison between PORT and CTRT at the fourth week of therapy, C.albicans was found to be 45.4% at fourth week of PORT, whereas in post CTRT, it was 50%. Among the non-albicans group, C. tropicalis, C.krusie, C.sacharavesie and T. asahii were the species found in 9.09% of patients in PORT group at the 4th week. In the post CTRT group at the 4th week, C. tropicalis was 40% and C. glabrata 10% were present. (Table 1).

The prevalence of candida albicans species to be 45.4% and 60% in the oral cavity of patients prior to undergoing PORT and CTRT, whereas, the incidence of non albican species was 27.27% and 50% in PORT group and CTRT group. The difference among the candida and non-candidal species between the PORT and CTRT prior to therapy was not statistically significant (p = 0.90 and p=0.7) (Table 2)

During the fourth week of follow up, results showed that Candida albicans species were present in 45.4% and 50% of the patients in the PORT and post CTRT groups respectively. The incidence of non-albican species were also higher with 45.4% and 50% in the PORT and post CTRT groups, there was no statistical significance in Candida species on comparison between both groups across treatment modalities. (p= 1) (Table 3)

Table 1.Identification of Candidal and other fungal species among patients undergoing various modes of therapy.

Candidal Species Identified	**Patients identified with species in PORT = 11**		**Patients identified with species in combinaton of Chemo and Radiotherapy = 10**	
	Prior to PORTn (%)	4th week after PORT	Prior to CT	4th week after CT
C. albicans	5 (45.4%)	5 (45.4%)	6 (60)	5 (50)
C.tropicalis	0	1 (9.09)	0	4 (40)
C. Krusie	1 (9.09)	1 (9.09)		
C. glabrata	1 (9.09)	0		1(10)
C. Parapsilosis	0	0	1(10)	0
C. sacharavesie	1 (9.09)	1 (9.09)		
Trichosporonasahii	0	1 (9.09)	0	0
C. famata	0	0	1 (10)	0

Table 2.Comparison of Candida albicans and non-albicans species among PORT and CTRT prior to therapy

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Candidal species	PORT	CTRT	P value
C. albicans	45.4%	60%	0.9
Non-albicans	27.27%	50%	

Table 3.Comparison of Candida albicans and non-albican species among PORT and CTRT at 4 weeks

Candidal species	PORT	CTRT	P value
C. albicans	45.4%	50%	1.03
Non-albicans	45.4%	50%	

With regard to grade of mucositis, Grade II mucositis was present in a higher percentage than grade I or grade III. 80% in the PORT group and 60% in the post CTRT group had Grade II mucositis , which was not statistically significant (p= 0.27).. There were no grade IV mucositis seen in our patients (Table 4)

Table 4.Comparison of mucositis among PORT and CTRT at 4 weeks

	PORT	CTRT	p-value
Grade II mucositis	80%	60%	0.27

The evaluation of Candida albicans in terms of CFU is given in the table below:

Table 5.Evaluation of Candida albicans in CFU

	Groups	Min CFU/mL (Mean)	Max CFU/mL (Mean)
C. Albicans count at baseline	RT = 20	50	1795
	CRT = 20	45	1750
C. Albicans count at 4^{th} week	RT = 20	75	2500
	CRT = 20	65	2450

C.albicans was found to have 97% sensitivity to fluconazole and non-albicans was 73%. C. albicans and non-albicans species was 100% sensitive to voriconazole, capsofungin and

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itraconazole. C. albicans was 100% sensitive to flucytosine whereas non albicans was 91.7% sensitive to flucytosine.C.albicans was 100% sensitive to amphotericin and non albicans showed 89%. (Fig 1)

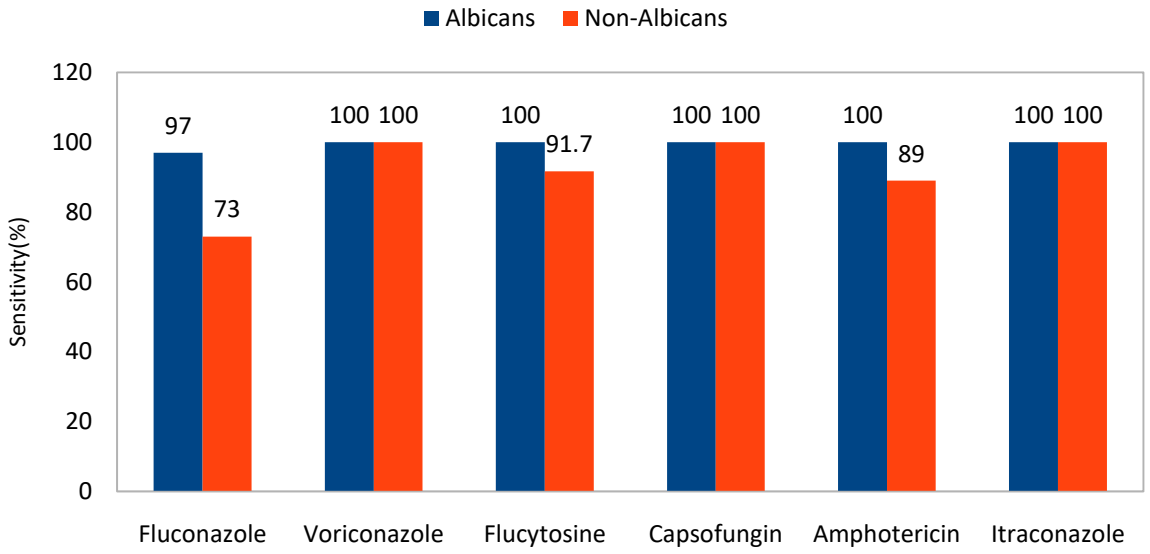

Figure 1: **Sensitivity of fungal organisms to antifungal drugs**

C.albicans was 3% resistant to fluconazole and non-albicans showed 24.3% resistance. Both albicans and non-albicans species showed 0% resistance to voriconazole, capsofungin and itraconazole. Non albicans showed 2.8% resistance to flucytosine and 8.3% to amphotericin.(fig 2)

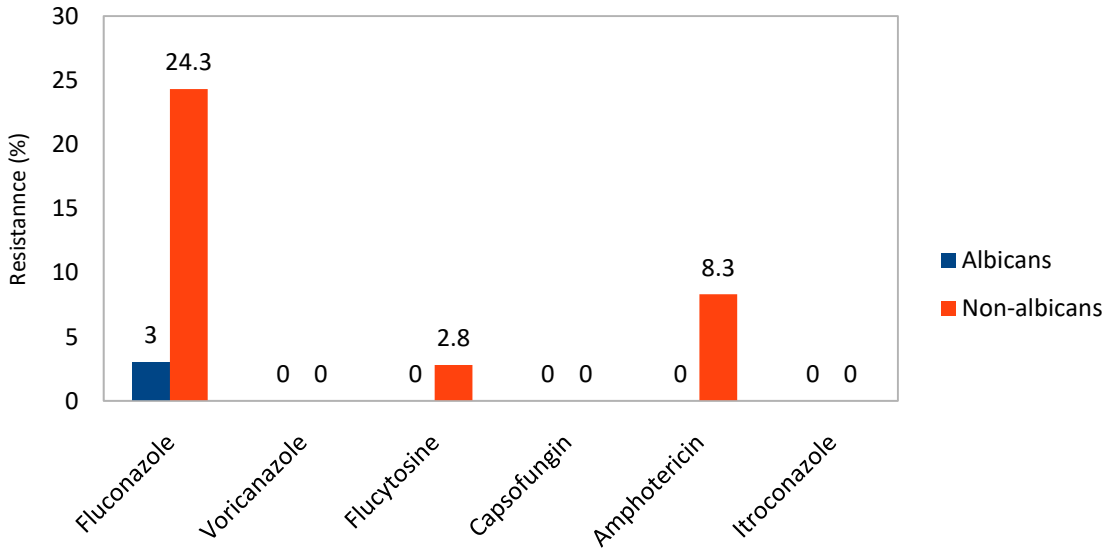

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Figure 2: Resistance of the fungal organisms to antifungal drugs

Discussion

Cancer patients who receive radiotherapy and/or chemotherapy are always at a risk of developing fungal infections in oral cavity than general population.The risk for oral candidiasis to spread to oropharyngeal regions and even systemic circulation is higher & is associated with immunosuppressed cancer patients.[7]

In our study, along with candida albicans which is the most common among fungal species, other non albicans species like tropicalis, krusie, glabrata, parapsilosis,sacharavesie were present but in minimal numbers.

Preethi L, et al[8] in their study of 20 patients, found that C albicans was the most commonly detected species at the baseline of RT alone constituting 58.3 % of the species. While, the non albicans species detected include C. krusei (25%) and C.tropicalis (16.6%).Azizi and Rezaei, et al[9] reported prevalence of different types of Candida before radiation therapy and their study of 20 patients revealed the percentages of C. albicans, C. krusei and C. tropicalis as 35%, 5% and 10%**.**

In the present study,the prevalence of C. albicans species was found to be 45.4% and 60% in the oral cavity of patients prior to undergoing PORT and CTRT respectively. The presence of non albican species prior to radiotherapy in PORT and CRT group was 27.27% and 50% respectively. The percentages indicate an increased prevalence of both candidal and non candidal organisms in patients prior to undergoing chemotherapy butthe difference was not statistically significant. Non albicans detected in the present study were tropicalis, krusie, glabrata and sacharavesie in the PORT group, al at less than 10%. In the CTRT group the non albicans species identified were tropicalis, glabrata, parapsilosis and famata at 10% each. C.tropicalis were seen only at the 4th week of PORT(9.09%) and CTRT(40%). C.tropicaliswas the most common non-candida albicans candida in our study which is consistent with other studies.[10] Only 10% of subjects had C.glabrata and kruseiin the present study.

With regard to patients receiving CTRT cis-platinum chemotherapy during radiation, Ramirez – Amador et al, documented that C. albicans represented 85 % of candidal organisms at the baseline of radiation therapy.[8]In the present study, C.albicans prior to CTRT was 60%

During the radiation therapy at fourth week, our results showed that Candida albicans species was present again in 45.4% of patients and 50% of the patients in the post CTRT groups respectively. Although, the C.albicans species percentages remained almost same in PORT and CTRT patients both prior and during the treatment, the non albicans species had increased in PORT group which was 27.7% to 45.4%. In CTRT group it was the same at 50%.

In the present study, mixed cultures of C.krusei and C.tropicalis along with C.albicanswere obtained and were noted in 7 patients in PORT group and 6 patients in CTRT group. For avoiding confounding these data were not incorporated. This was similar to findings

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by Preeti et al. Preethi L, et al also reported that, at the end of radiation therapy C. albicans constituted 80% of the species, whereas C. krusei was 5% with the rest detected as mixed cultures.[8] It was seen that C tropicalis was present in both the single as well as in the mixed species culture.

Azizi and Rezaei, et al reported prevalence of different types of Candida among 20 patients during second week of radiation therapy, revealed the percentages of C. albicans, C. krusei and C. tropicalis as 60%, 15% and 15% respectively. The cultures of C.krusei and C. tropicalis had mixed growth with C. albicans.[9]

Belazi MV, et al showed C. albicans was the predominant species isolated in 59% of the patient undergoing radiotherapy in their study. The non albicans species identified in the fourth week were C. glabrata (8%), C. kefyr (5%), C.tropicalis (3%), and C. Krusei (3%).[11]

Ramirez – Amador et al, documented that C. albicans represented 68 % of candidal organisms at the completion of CTRT[12].In the present study no C. albicans species were found in 2 of our patients in RT group and 4 patients in CRT group. However, we could not identify any study from literature review that has reported absence of candidal species in saliva samples. Merlano et al, in their series of 157 patients with inoperable head & neck carcinoma who had undergone either CTRT or RT as primary treatment reported that, 34% of the patients had Grade I mucositis in CTRT group and 35% in RT group. 15 % in the CTRT group and 25% in the RT group had Grade II mucositis. Also, Grade III mucositis was prevalent in 16% of patients from CTRT alone group and 17% from RT group.[13]

With regard to grade of Mucositis, 10 % of our patients had Grade I mucositis in both PORT and CTRT groups during therapy. 80% in the PORT group and 60% in the CTRT group had Grade II mucositis.Grade III mucositis was prevalent in 10% of patients from PORT group and 30% from CTRT group. These differences were not statistically significant. It can be inferred that radiotherapy seems to be a great inducer of mucosal damage, leading to more permanent changes than chemotherapy,where the oral alterations are for ashort duration.

The present study was similar in the results of grade 1 mucositis when comparing with that of Merlano et al's study.[14] However, a difference of about 20% with regard to Grade III mucositis was seen when comparing. Radiation induced mucositis can cause PORT interruptions and failure of local disease control. 4 patientsin our study had been placed on PEG tube due to severity of mucositis as they had difficulty in intake of normal foods. 3 of these patients were in CTRT group whereas 1 was in RT group and all were dentate. Redding et al stated that dentate patients had more grade of mucositis as it causes trauma and ulceration of radiation damaged oral mucosa.[15]

Spijkervet et al[16] also reported the incidence of oral candidiasis along with mucositis where the highest score was observed after 3 weeks of radiotherapy i.e., approximately 30 grays. In the present study also,patients had either grade 1, 2 and 3 mucositis along with candidiasis in the 4th week of evaluation after PORT.

None of our patients had Grade IV mucositis.Intervention with oral corticosteroids and pain relievers was doneat Grade III mucositis stage.

The reduction of ulcerative mucositis to minimize unplanned breaks in radiotherapy may enhance tolerability & efficacy. Several strategies to prevent ulcerative mucositis in radiotherapy for head and neck cancers have been evaluated, but none have demonstratedstrong efficacy.[17] In our study,15% of patients in the post op RT group and 20% post CTRT group had treatment breaks. 2 of our patients had varicella zoster infections, 2 had pulmonary TB, 2 had breaks due to fever and fatigue.

The occurrence of candida species in oral cavity of cancer patients necessitates effective

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management of infection with antifungal medications prior to anticancer therapy. In our study, the sensitivity of candidal and non candidal species to different systemic antifungal drugs like fluconazole, voriconazole, flucytosine, capsofungin, amphotericinB and itraconazole, were determined. It was found that all isolates,candidal and non candidal were 100% susceptible to voriconazole, capsofungin and itraconazole.Belazi M et al, reported that the candida isolates had very low voriconazole MICs in their study.[11] In this study, Calbicans,Krusie and glabrata were found to be resistant to itraconazole.C. krusei strains were resistant to fluconazole in all the 6 samples. This finding is similar to that of the studies by Bulacio L et al[10] and Grotz KA,[18] et al.

C. albicans, C. famata, C. parapsilosis, C. sacharavesie, C. pelliculosa were found to be 100% sensitive to Flucytosine. Non-candida species like kodamaeaohmeri, T.asahii, kluekara species were also found to 100% sensitive to Flucytosine. Only 80% of C. tropicalis were sensitive and 20% with intermediate sensitivity to flucytosine. 67% of C. krusie were sensitive to Flucytosine and 33% were resistant.

C.albicans, C.glabrata, C.famata, C.parapsilosis and C. pelliculosa were found to be 100% sensitive against Amphotericin B. Among the non-candidal species, K. ohmeri and kluekara species were 100% sensitive to Amphotericin. Other Candidal species like C. tropicalis, C. krusie and C. sacharavesie showed 92%, 80% and 50% sensitivity respectively to Amphotericin.

Our study, representative of the Indian population, as in all studies done elsewhere in the world, found the fungal organism, C.albicans to be the predominant species present in the oral cavity of cancer patients. Non albicans species were seen as single and mixed species in the saliva samples, both prior and during treatment. Culture sensitivity of fungal organisms revealed three antifungal drugs, namely voriconazole, capsofungin and itraconazole, that could be used as prophylactic measures in the prevention of candidiasis and mucositis.

Conclusion

In the present study involving patients undergoing cancer therapy, multiple species of fungal organisms were identifiedboth prior and during treatment with Candida albicans as the most common species identified, followed by non albicans species like C. tropicalis,C. krusie, C.glabrata andC.parapsilosis. Non candida species were also present in the patients. Among the non albicans species, C tropicalis was the most common. Mixed species were detected in samples taken from patients both prior and during treatment. However, there were no statistical difference between species obtained prior to and species obtained during treatment or when compared between two treatment modalities.

Assessment of mucositis in our patients showed an increased percentage of grade 2 mucositis in both treatment modalities.

Sensitivity profiles of candidal species revealed that all candidal and non candidal species were hundred percent sensitive to the antifungal drugs likevoricanozole, capsofungin anditraconazole. Studies assessing the treatment outcomes from interventions with antifungal drugs, could further help in better patient management

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