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ORIGINAL ARTICLE

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Treatment modalities for oral verrucous carcinomas and their outcomes: contribution of radiotherapy and chemotherapy

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Abstract
Background. This clinical study focused, firstly, on the results of treatment and, secondly, on the anaplastic transformation, of oral verrucous carcinomas (OVCs) diagnosed and treated from 1981 to 1997 at the Department of Oral and Maxillofacial Surgery at Shimane Medical University Hospital.
Methods. We analyzed the treatment modalities and outcomes for 15 patients with OVC.
Results. Excluding the results for 4 palliatively treated patients, the disease-free survival rates of the patients after the initial treatments, were 82% at 5 years and 66% at 10 years; for all 15 patients, these rates were 57% and 46%, respectively. Surgery alone and surgery combined with other treatments (such as radiotherapy and chemotherapy) appeared to yield disease-free survival rates to those achieved superior with other treatments whether single or combined; (78% vs 33% for 5-year disease-free survival; 52% vs 33% for 10-year disease-free survival); however, the difference was not significant ($P = 0.47$). Well differentiated squamous cell carcinomas (W-SCCs) ($n = 5$) as well as spindle cell carcinoma ($n = 1$) were found in subsequent operative or biopsy specimens.
Conclusion. Surgery was the most reliable treatment method for OVC; however, radiotherapy combined with chemotherapy was the next most preferable treatment when surgery was not undertaken. We also found that highly malignant transformation (anaplastic transformation) occasionally occurred during treatments for OVC.

Key words Oral verrucous carcinoma · Treatment modality · Combination of radiotherapy and chemotherapy · Prognosis · Anaplastic transformation

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Introduction

Verrucous carcinoma (VC), a distinct variant of well differentiated squamous cell carcinoma (W-SCC), is now accepted as having the following clinical features:[1–3] (1) most lesions occur in elderly persons; (2) the oral cavity is one of the predilective sites; (3) the lesion gradually shows an exophytic nature, with a whitish-to-gray shaggy surface; (4) the lesion grows into surrounding tissues in a pushing fashion, and, if it is untreated, gradual invasion of underlying bone occurs and the lesion eventually metastasizes to the regional lymph nodes; (5) surgical methods are generally used as the primary therapy; and, (6) the prognosis of oral VC (OVC) is generally good.

Nowadays, no one doubts that the most suitable method of treatment for OVC is complete removal, similar to the treatment of other malignancies.[1–10] However, since the first report by Ackerman in 1948,[1] there have been ongoing discussions regarding the optimal therapy for OVC. The fundamental point of this discussion has focused on highly malignant or anaplastic transformation after radiotherapy.[6–10] The older literature clearly stressed this point and even expressed opposition to radiotherapy.

Gradually, however, radiotherapy has gained credibility in the treatment of OVC.[2,3,11] Recent articles show rather better results than earlier reports, with disease-free 5-year survival of 49% to 66% in many case analyses.[3,11]

Chemotherapy, including cytotoxic drugs such as 5-fluorouracil, bleomycin, and methotrexate, has also had positive reports as an efficient treatment for OVC.[4] These drugs showed clear beneficial effects, particularly in reducing tumor size,[12] but have generally failed to produce complete remission.

An report by Yamamoto et al.;[4] however, revealed good results for the treatment of OVC with chemotherapy: a 60-year-old Japanese woman with widely extended OVC in the bilateral soft and hard palate, the left pterygomandibular raphe and retromolar portions, the left buccal and lower alveolar-gingival mucous membranes, and in the left side of the floor of the mouth, had been treated with three courses

of CPE chemotherapy (combination chemotherapy with cisplatin, peplomycin, and etoposide); at the time of the report, she was healthy with no recurrence 2 years and 3 months after completion of the treatment. Such results encourage us to treat widely extended OVC by nonsurgical methods.

We have been treating OVC patients with surgery, radiotherapy, and/or chemotherapy, and now confirm that combinations of radiotherapy and chemotherapy are effective in some OVCs. We believe that, occasionally, clinicians must select nonsurgical treatment methods in some OVCs because of widespread extensions or multiple lesions, the patient's poor medical condition, or the patient's wish not to undergo surgery.

Treatment results from our clinic are presented and discussed here, as is the anaplastic transformation of OVC.

Patients, materials, and methods

At the Department of Oral and Maxillofacial Surgery at Shimane Medical University Hospital, 15 patients (5 men and 10 women) aged from 62 to 96 years at the time of first examination (median age, 76.9 years) were histologically diagnosed as having OVC either before the initial treatment or at the time of the first surgical treatment. They were treated with any one of or any combination of surgery, laser vaporization, chemotherapy, radiotherapy, and/or immunotherapy (administration of OK-432 [biological response modifier; Chugai Seiyaku, Tokyo, Japan]) from April 1981 to January 1997. Generally, biopsies were carried out on more than two different portions in multiple or extended lesions.

Tumor size (T) was determined using the TNM classification recommended by the International Union against Cancer (UICC) (1997)[13] based on clinical and imaging findings. At initial presentation, 6 patients were seen with T2, 1 patient was seen with T3, 5 patients were seen with T4, and 3 were seen with multiple lesions. No patients were diagnosed as having regional lymph node or distant metastasis at the first examination. The clinical and pathological features of the patients are listed in Table 1.

The accepted policy in our department was excision as the treatment of first choice for OVC; however, the patient's wishes and other existing medical problems also played a part in determining treatment modalities. As a chemotherapy treatment alone, peplomycin was generally administered solely, at a dose of 5 mg/once daily $\times$ 5 days via the venous route, or UFT (uracil + 1-(2 tetrahydrofuryl)-5-fluorouracil) was given orally (three tablets per day). One tablet of UFT contained 100 mg of tegafur and 224 mg of uracil. We determined the effect of UFT only in patients in whom it was administered for more than 6 months. Combination chemotherapy with cisplatin (from 100 to 130 mg) and 5-fluorouracil; 5-Fu) (250 mg $\times$ 4 days) and also combination chemotherapy of cisplatin (100 mg), peplomycin (5 mg $\times$ 5 days) and Oncovin (1 mg; vincristine; VCR) were carried out. Radiotherapy was carried out as external irradiation; external beam radiation was delivered using a 4-MV accelerator at a dosage schedule of 2 Gy per lesion once daily $\times$ 5 days/week. We generally tried to irradiate the primary lesion using radical and curable dosage as a goal. Patients receiving radiotherapy actually received a total of 43.2 to 70 Gy (Table 1). Intracavitary irradiation was also carried out, using a 4-MeV electron beam.

With regard to the combination of radiotherapy and chemotherapy, irradiation was done under continuous administration of 5-Fu to the lesion of the palatal and upper gingival OVC through the maxillary artery by cannulation to the superficial temporal artery. At the same time, necrotic tissues of the lesion were removed by aspiration or vacuum suction.

Immunotherapy was not evaluated for its efficiency because of the unclear response to OVC and because no patients were treated solely by immunotherapy. The laser vaporization carried out in one patient (case 15) was included in the nonsurgical treatments because of its palliative application.

The treatments that each patient underwent were rather complex; therefore, in there we divided them into the surgery group (n = 9), covering surgical treatment in any period, and the nonsurgery group (n = 6) which includes chemotherapy, radiotherapy, immunotherapy, and laser vaporization.

Analysis of survival was performed by the Kaplan-Meier method, using Statview software (SAS Institute, Cary, NC, USA), and the Mantel-Cox test was used to determine the significance of differences between the surgery and nonsurgery groups.

Results

Initial treatments and their outcomes

Excision of the lesions was undertaken first of all, if possible. When surgery was not performed, radiotherapy or chemotherapy alone, or a combination of these modalities, was selected.

As shown in Table 1, of the 15 patients, 4 patients underwent surgery only, 1 patient had radiotherapy only, 4 patients received chemotherapy only, 3 had a combination of surgery and chemotherapy, and 3 had a combination of radiation and chemotherapy. These initial treatments completely controlled OVC in 5 patients for periods of 2 years and 2 months to 11 years and 11 months; 2 of the 5 patients (cases 1 and 2) were surgery-only, 1 patient (case 8) had surgery/chemotherapy; and 2 patients (cases 11 and 12) had radiotherapy and chemotherapy. Four patients (cases 3, 9, 10, and 14) had recurrences, at periods of 1 month to 2 years and 2 months after the treatments.

Residual OVC after the initial treatments was diagnosed in 5 of the 15 patients (cases 5, 6, 7, 13, and 15). In case 13, metastasis to the regional lymph nodes, as well as primary recurrence, became evident clinically during chemotherapy;

Table 1. Clinicopathological features of oral verrucous carcinoma (OVC) involved in this study

Case no.	Age[a] Sex	Location	Tumor condition (size)[b]	Initial treatment	Recurrence or residual after primary treatment	Histology (first biopsy)	Treatments for recurrent or residual tumor	Histological change after treatments	Follow-up status (last examination)	Duration of follow-up[c]
Surgery alone										
1	81/F	BM	T2	S (Tumor excision)	(−)	VC			A without OVC	2 Y 2 M
2	70/M	LAM	T2	S (Tumor excision)	(−)	VC			A without OVC	6 Y 10 M
3	62/F	TM	T2	S (Tumor excision)	Recurrence (2 Y 2 M)	VC	S (Tumor excision)		A without OVC	4 Y 8 M
4	65/F	BM	T3	S (Tumor excision)	Metastasis to the SMLN (6 M)	VC	SHND	W-SCC	A without W-SCC	3 Y 1 M
Chemotherapy alone										
5	82/F	BM, LAM, MFM	T4	C (PEP, 100 mg)	Residual tumor	VC	Not done		D with OVC	7 M
6	91/F	UAM, HPM	Multiple lesions	C (UFT, 3 tablets/day)	Residual tumor	VC	Not done		D with OVC	7 M
7	96/F	ULM, UAM, BM, RM, LAM, HPM, SPM	T4	C (UFT, 3 tablets/day)	Residual Tumor	VC	Not done		D with OVC	1 Y 11 M
Surgery and chemotherapy										
8	63/F	UAM, BM	T2	S (Tumor excision) C (CDDP, 100 mg + PEP, 25 mg + Oncovin (vincristive; VCR; 1 mg)	(−)	VC			A without OVC	11 Y 11 M
9	82/F	LAM, MFM, BM	Multiple lesions	C (UFT, 3 tablets/day) S (Partial tumor removal)	Recurrence (1 Y)	VC	Not done	W-SCC	D of W-SCC	2 Y 2 M
Radiotherapy (and surgery after recurrence)										
10	88/M	BM	T2	R (70 Gy)	Recurrence (2.5 M)	VC	S (Tumor excision + SHND)	W-SCC	D without W-SCC	7 Y 9 M

Table 1. Continued

Case no.	Age[a] Sex	Location	Tumor condition (size)[b]	Initial treatment	Recurrence or residual after primary treatment	Histology (first biopsy)	Treatments for recurrent or residual tumor	Histological change after treatments	Follow-up status (last examination)	Duration of follow-up[c]
Radiotherapy and chemotherapy										
11	77/M	BM	T2	R (50 Gy) C (UFT, 3 tablets/day)	(−)	VC			A without OVC	8 Y 1 M
12	67/M	BM, RM, LAM	T4	R (43.2 Gy) C (5-Fu, 5400 mg)	(−)	VC			A without OVC	11 Y 3 M
Radiotherapy, chemotherapy, and surgery or laser vaporization										
13	66/M	BM, LAM, RM	T4	C (5-Fu, 2000 mg; CDDP, 130 mg + 90 mg; UFT, 3 tablets/day) S (Tumor excision + RND[d])	Residual tumor	VC	R (50.4 Gy)	W-SCC	D of W-SCC	6 M
14	78/F	UAM, BM, SPM, HPM	T4	R (50.4 Gy) C (5-Fu, 8000 mg)	Recurrence (1 M)	VC	S (maxillectomy)	W-SCC	D without W-SCC	10 Y 10 M
15	89/F	BM, UAM, RM, HPM, SPM	Multiple lesions	C (UFT, 3 tablets/day)	Residual tumor	VC	R (36 Gy + 39 Gy[e]) + LV (4 times)	Spindle cell carcinoma	D of spindle cell carcinoma	3 Y 3 M

[a] Age at first examination
[b] T size follows the TNM classification of malignant tumors presented by the International Union against Cancer (UICC); 1997)[13]
[c] Time from the initial treatment to the most recent examination
[d] Metastasis to the submandibular lymph node was proven histologically
[e] Intra-cavitary irradiation
BM, Buccal mucosa; TM, tongue mucosa; MFM, mucosa of the mouth floor; SPM, soft palate mucosa; HPM, hard palate mucosa; UAM, upper alveolar mucosa; LAM, lower alveolar mucosa; RM, retromolar mucosa; SMLN, submandibular lymph node; W-SCC, well differentiated squamous cell carcinoma; VC; verrucous corcinoma; OVC, oral verrucous carcinoma; A, alive; D, died; LN, lymph node; R, radiation therapy; S, surgery; LV, laser vaporization; C, chemotherapy; SHND, suprahyoid neck dissection; RND, radical neck dissection; Y, year; M, month
PEP, peplomycin; CDDP, cisplatin; 5-Fu, 5-fluorouracil; UFT, uracil + tegafur (see text for details)

therefore, radical neck dissection plus primary excision was carried out promptly. This revealed histological evidence of metastasis to one of the submandibular lymph nodes.

The OVC in case 4 was curably excised, but metastasis was evident 6 months after the excision; neck surgery was required subsequently.

Six of the ten patients who required further treatments (i.e., those with residual tumor or recurrence) underwent second treatments (Table 1), but the remaining four patients (cases 5, 6, and 7 who underwent chemotherapy alone, and case 9 who was treated with chemotherapy and surgery) underwent no further treatments. The second treatments administered to the six patients are described below.

Second or subsequent treatments and their outcomes in six patients

Four patients with recurrence (cases 3, 4, 10, and 14) were surgically treated. Primary recurrent lesions in two of these patients (cases 3 and 14) were excised and they were completely controlled (Table 1).

In the two remaining patients (cases 4 and 10), submandibular lymph node metastasis was strongly indicated by imaging and clinical examinations. However, both the metastasis and the recurrence in these two patients were diagnosed as being at submandibular level in a single lymph node in each patient. These findings in cases 4 and 10 indicated the need for at least suprahyoid neck dissection. Additionally, case 4 had been suffering from chronic renal failure, Parkinson's disease, and chronic hepatitis C, while case 10 was elderly and not in good general condition. Therefore, a lengthy surgical procedure was not desirable in either patient. Suprahyoid neck dissection (SHND) was performed in case 4, and SHND plus excision of the recurrent SCC was carried out in case 10, rather than complete radical neck dissection. Metastasis of one submandibular lymph node, without extracapsular spread, was revealed histologically in case 4, while no metastasis was shown in case 10. The patients were well controlled for 3 years and 1 month and 7 years and 9 months, respectively.

Cases 13 and 15 underwent radiotherapy without being controlled. As follow-up treatment, laser vaporization was carried out in case 15.

Four patients without subsequent curative treatment

Of the four patients, without subsequent curative treatment, three (cases 5, 6, and 7) died with OVC, and one (case 9) died of W-SCC.

Age, total treatment modalities, and their outcomes

Surgical treatments were carried out at various ages in nine patients, whenever the lesions were diagnosed as needing complete removal. Four patients (cases 3, 4, 8, and 13) in their sixties; two patients (cases 2 and 14), in their seventies; and three patients (cases 1, 9, and 10) in their eighties were controlled completely either by surgery alone (cases 1, 2, 3, and 4), combined treatment of surgery and chemotherapy (case 8), initial radiotherapy and surgery after recurrence (case 10), radiotherapy and chemotherapy (cases 11 and 12), or radiotherapy and chemotherapy following surgery after recurrence (case 14). Four patients (one in his sixties and three in their eighties) were not controlled (cases 5, 9, 13, and 15). The two remaining patients (cases 6 and 7) who were both aged over 90 years were treated only palliatively with chemotherapy, and died with OVC.

Tumor size, all treatment modalities, and outcome

T2 and T3 lesions diagnosed at the first examination were all effectively treated either by surgery alone (cases 1, 2, 3, and 4), incipient radiation and surgery after recurrence (case 10), a combination of surgery and chemotherapy initially (case 8), or an incipient combination of radiation and chemotherapy (case 11). All of these patients have been free of OVC or W-SCC for periods ranging from 2 years and 2 months to 11 years and 11 months (Table 1).

In contrast, of the remaining eight patients, of whom five (cases 5, 7, 12, 13, and 14) had T4 lesions, and three (cases 6, 9, and 15) had multiple lesions, only two patients (cases 12 and 14) with T4 lesions have been free of OVC, for 11 years and 3 months and 10 years and 10 months, respectively. These two patients (cases 12 and 14) were treated with combinations of radiotherapy and chemotherapy initially, and combinations of incipient radiotherapy, chemotherapy, and surgery after recurrence.

Three of our 15 patients died with OVC (cases 5, 6, and 7), 2 died of W-SCC (cases 9 and 13), and 1 died of spindle cell carcinoma (case 15) (Table 1).

The overall disease-free survival in our 15-patient population was 57% at 5 years after the initial treatments and 46% at 10 years. When the results for the 4 patients with palliative treatments were omitted from this population analysis, the survival rate was 82% at 5 years and 66% at 10 years (Fig. 1).

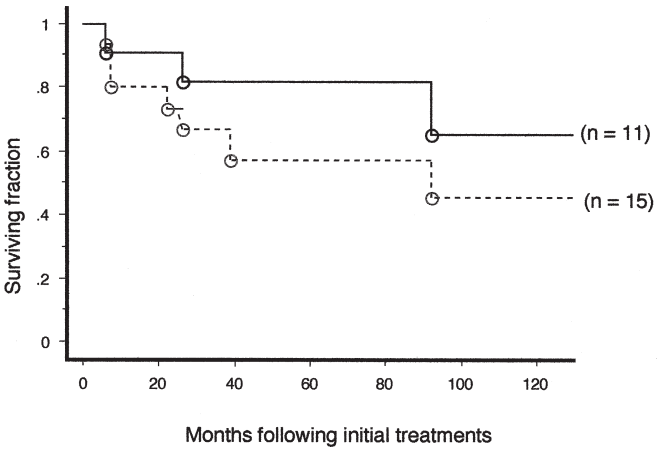

Fig. 1. Disease-free survival curves after initial treatments for patients with active treatments (—; $n = 11$), and in all patients (----; $n = 15$)

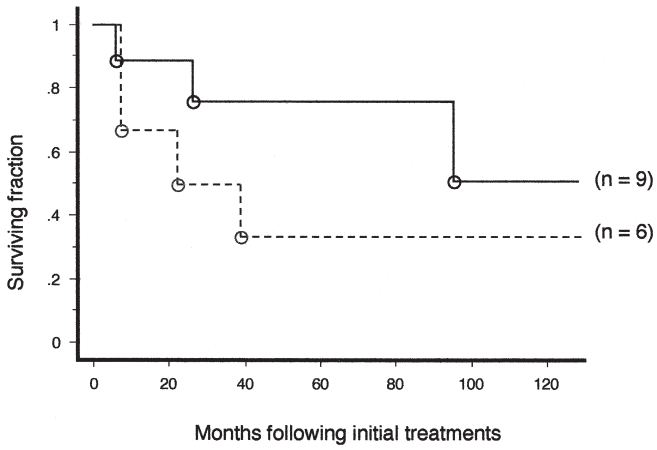

Fig. 2. Comparison of disease-free survival rates between patients treated with surgery alone, or surgery combined with radiotherapy, or chemotherapy, or combined with both these modalities (surgery group; — $n = 9$), and those patients treated with therapies other than surgery (nonsurgery group; --- $n = 6$). No significant difference was observed between the surgery and nonsurgery groups ($P = 0.47$; Mantel-Cox test)

Outcomes for different treatment modalities

When the patents were divided into surgery ($n = 9$) and nonsurgery groups ($n = 6$), the disease-free survival rates were 78% at 5 years and 52% at 10 years for the surgery group, and 33% at 5 years and 33% at 10 years for the nonsurgery group. Cure of OVC seemed to be brought about more frequently by surgery, but no significant difference was shown between the two groups (Fig. 2). It is worth noting that radiotherapy combined with chemotherapy in cases 11 and 12 also brought about complete cure, for 8 years and 1 month and 11 years and 3 months, respectively (Table 1).

Treatment modalities; pathologies; durations between initial OVC diagnoses and surgery

All 15 patients showed VC either at the first biopsy (n = 12) or in the first operated materials (n = 3). However, subsequent biopsies carried out after the treatments, or histological examination of the first resected materials, revealed W-SCC in 5 patients (cases 4, 9, 10, 13, and 14).

In one of these five patients, case 4, the duration between the first biopsy and the excision was 36 days, during which time we evaluated the patient's general condition and carried out no other treatments. It was judged that OVC and W-SCC already coexisted at the time of the first examination in case 4.

For the remaining four patients, the durations between the first biopsy and surgery were 14 months and 16 days (case 9), 4 months and 28 days (case 10), 2 months and 15 days (case 13), and 3 months and 18 days (case 14). In these four patients, we were unable to determine whether the OVC and W-SCC coexisted at the time of the first examination or whether malignant transformation had occurred.

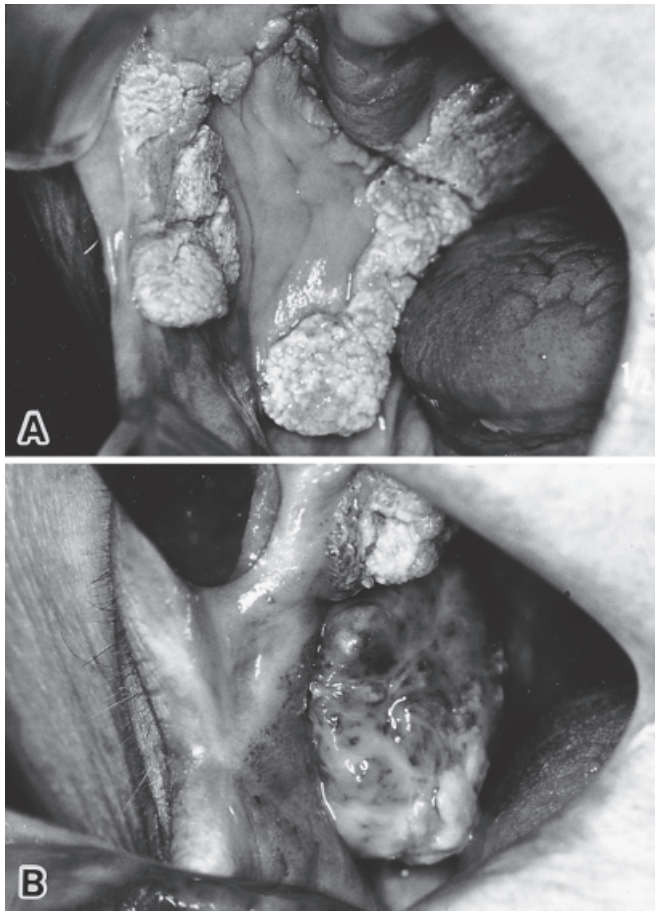

Fig. 3. **A** Multiple verrucous carcinoma of the oral mucosa at the initial examination (case 15). **B** A fast-growing tumor developed in the right buccal mucosa, corresponding to the upper first molar

A clear anaplastic change of OVC to spindle cell carcinoma (case 15) was observed in one patient (Figs. 3 and 4). The period between the first diagnosis of OVC and histologic recognition of spindle cell carcinoma was 44 months and 15 days.

In 3 of our 15 patients (cases 4, 10, and 13), the tumors were highly suspected to have metastasized to the regional lymph nodes, but in only 2 of the 3 patients, was there histological confirmation of metastasis to the submandibular lymph nodes (cases 4 and 13).

Discussion

The most preferable treatment for OVC is local excision – marginal or segmental resection for a tumor showing fixation to the alveolar portion or invasion of the underlying bone, and neck dissection for cervical metastasis or when there is suspicion of metastasis. This is because invasive SCC may sometimes lurk beneath or coexist with an apparent OVC.[1,5,8,11]

A review of the treatment modalities for OVC shows that radiotherapy,[2,3,11,14,15] chemotherapy,[4,16] combinations of

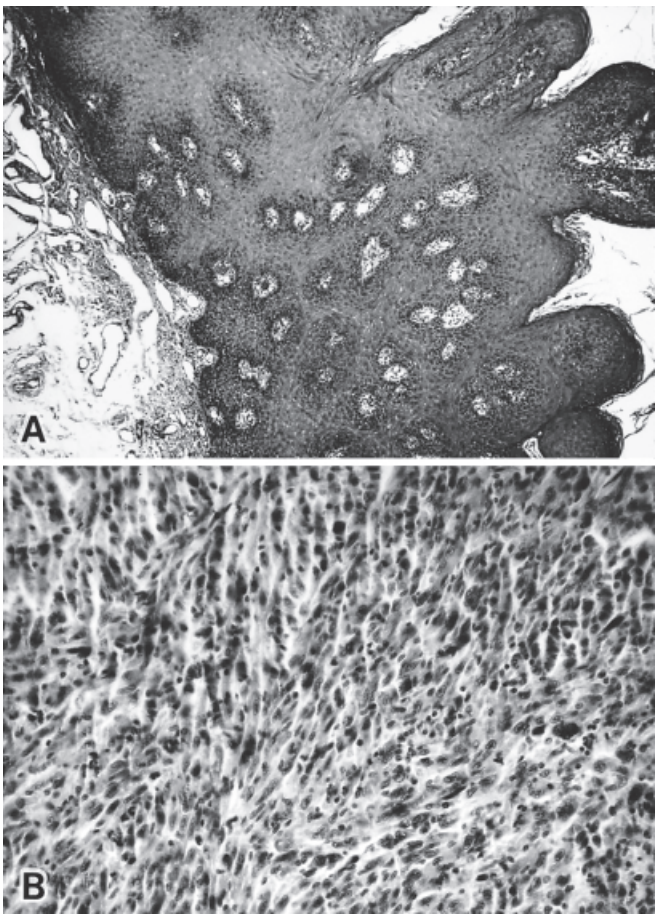

Fig. 4. **A** Biopsy sample from the first examination shows verrucous carcinoma. **B** Recurrent tumor, showing spindle cell carcinoma. **A** H&E, ×40; **B** H&E, ×100

these two modalities,[6,8,12] and other nonsurgical treatments[12,17] have also been employed, probably because the lesions were extensively overgrown, or because the patients had medical problems ruled out a radical operation, or because the patients did not wish to undergo operative treatments. We also noted specific treatment modalities for VC in the literature, such as photodynamic therapy,[17] administration of bleomycin (BLM),[16] cryosurgery,[18] laser surgery,[19,20] and the administration of recombinant alfa-interferon.[12] These methods may be acceptable for some OVCs, but their "efficiency" has yet to be established because of the few patients treated by each method.

The remarkable finding in our report is that combinations of radiotherapy and chemotherapy made it possible to completely control the patients' OVC in two patents (Table 1). Thus, we are now of the opinion that, although treatment methods naturally differ with each OVC patient, combined treatment with radiotherapy and chemotherapy is a viable choice. Additionally, from a practical standpoint, we continue to need radiotherapy, chemotherapy, and other treatment modalities, because OVCs extending over a wide range or occurring in multiple regions are difficult to excise completely.

We are unable to make valid comparisons of the results of treatment in this study with results from other studies in the literature because of different methods of calculation and different standards for treatment effectiveness. For example, the control rate with surgery reported in the literature ranged from 71% to 94% (Table 2),[5,7,8] while for radiotherapy, the reported overall 5-year survival rates ranged from 49% to 86% (Table 2).[2,3] However, the standards in these studies were undefined, so we cannot make a comparison.

The 5-year survival rate reported by Goethals et al.[21] was 76.4%. In the evaluation of their various treatment methods, diathermy produced a 75% survival rate, diathermy and radiotherapy a 66.7% rate, and excision a 71% rate.[21]

The report of Kraus and Perez-Mesa[7] revealed that, of 105 patients with VC of the oral cavity, larynx and genitalia, 88 were treated surgically and 17 received radiation therapy; there was recurrence in 9 of the 88 patients (10.2%) treated surgically by such methods as excisional biopsy ($n = 2$), local excision ($n = 67$), and excision with neck dissection ($n = 19$), and 3 patients treated by surgery subsequently died of VC. It is noteworthy that all patients ($n = 17$) with radiation therapy experienced recurrence.[7] As for patients with OVC only (64 patients), surgery achieved 94% ($n = 60$ patients) control.[7] Seven of 13 patients with recurrent OVC after radiation therapy underwent surgery, resulting in good control (54% effectiveness).[7]

On statistical analysis, our study did not demonstrate a clear superiority of the surgery group over the nonsurgery group, in part because of the limited number of patients.

The most important and problematic aspect of the treatment of OVC is the anaplastic transformation caused by radiation therapy (Table 3). The phenomenon was first reported by Perez et al.[6] in 1966, when they reported it to have occurred in 8 of 17 OVC patients. They reported that: (1) 3 of the 8 OVCs transformed into more malignant squamous cell carcinoma and the patients died of oral cancer; (2) the transformation occurred after high doses of irradiation (55 to 75 Gy); and (3) the OVC had been eliminated at least once clinically by radiotherapy, and had recurred after a short interval following irradiation.

Anaplastic transformation or more aggressive changes of VC may also occur as a result of chemotherapy, cryosurgery, laser surgery, and even after conventional multiple surgeries.[9,22,23] It has been conceptionally supported that the histological association of VC with less differentiated and potentially more aggressive carcinomas can occur;[24] further, we have experienced squamous cell carcinoma that developed into a less differentiated form upon recurrence or after various cancer chemotherapies. Demian et al.[8] reported a 28.9% rate of occurrence of anaplastic transformation within 6 months of the initial treatments. In 1982, McDonald et al.[9] reported transformation in 4 of 53 VCs (7.5%). Some of the reports listed in Table 3 revealed high rates of malignant transformation, as high as 37.5% (Table 3).[8–11] However, a recent review article by Ferlito et al.[25] reported only 10 (6.7%) cases of true anaplastic transformation among 148 lesions treated with irradiation in the head and neck. Orvidas et al.[11] noted no cases

Table 2. Outcomes of various treatment methods for OVC (1966–1998)

Authors (year)	Treatment methods	Number of treated patients	Patients with cure or controll	Outcomes and remarks
Kraus and Perez-Mesa (1966)[7]	Surgery Radiotherapy	64 13	60 (94%) 0 (0%)	Patients with short follow-up periods are included. All patients had recurrence. In 7 of these 13 patients, recurrent lesions were sucessfully excised. These figures are the final controlled numbers (%).
Demian et al. (1973)[8]	Surgery Radiotherapy Radiotherapy + surgery	7 1 3	5 (71%) 0 (0%) 2 (67%)	This group includes 2 patients with no treatment for recurrence. Two patients were free of OVC, for 4 years and 6 years, respectively.
Medina et al. (1984)[5]	Surgery Radiotherapy	90 12	85 (94%) 10 (83%)	These figures are the final controlled numbers.
Nair et al. (1988)[14]	Radiotherapy	50	22 (44%)	These 22 patients showed no recurrence. Thirteen of 15 patients who had recurrence and were treated by radium implant exhibited no recurrence for 3 years.
Vidyasagar et al. (1992)[2]	Radiotherapy	107	Stage I (100%) II (68%) III (35%) IV (26%)	These figures are disease-free 5-year survivals. The overall 5-year survival rate was 49%.
Jyothirmayi et al. (1997)[3]	Radiotherapy	53	Stage I (91%)[a] II (61%)[a] III (48%)[a] IV (0%)[a]	The actuarial 5-year survival rate was 66%, and overall 5-year survival rate was 86%.
Ferlito et al. (1998)[25]	Radiotherapy	148	64 (43.2%)	These lesions occurred in the oral cavity, nasal fossa, nose, larynx, and hypopharynx. These cases were gathered from the literature for this review article.

[a] The figures in each stage are actuarial 5-year survival rates

Table 3. Malignant or anaplastic transformation of OVC in patients treated with radiation or other cancer therapies

Authors (year)	Total no. of treated patients	No. of patients with more malignant or anaplastic transformation	Remarks
Kraus and Perez-Mesa (1966)[7]	16 (17)[a]	3 (4)[a]	Radiotherapy was the initial form of treatment in 17 patients and was unsuccessful in all.
Perez et al. (1966)[6]	8	3[b]	All 8 patients underwent radiotherapy. Three patients died of recurrent carcinoma within 1 year after the last treatment.
Fonts et al. (1969)[10]	10	3	Of the 3 patients with anaplastic transformation, 1 had radiotherapy alone and 2 had combined treatment with irradiation and surgery.
Demian et al. (1973)[8]	11	0	No anaplastic transformation was found in any of the 11 OVC patients.
McDonald et al. (1982)[9]	53	4	Of the 53, 22 were cured, 25 developed local recurrence, and 1 patient showed no response to treatment. In one additional patient with coexisting moderately differentiated epidermoid carcinoma, local recurrence occurred with rapid progression until death.
Tharp and Shidnia (1995)[15]	6	0	Six patients with OVC and 1 with laryngeal VC who underwent radiotherapy showed 71% local control. No anaplastic transformation occurred.

[a] One of these 4 cases was a nasal fossa lesion
[b] Included in the series by Kraus and Perez-Mesa[7]

of anaplastic transformation among 53 patients treated by irradiation.

In our present study, the initial histopathological feature of OVC changed to that of well differentiated SCC in five patients. However, we cannot say with certainly that the OVCs transformed to well differentiated SCCs after the initial diagnosis. It is possible that some lesions may have already been well differentiated SCCs at the time of the first examination, and that only the OVC portions of the lesions were obtained at the first biopsy. In any discussion of malignant transformation from OVC to various kinds of differentiated SCC, precise histopathological examinations of incipient, operated, and subsequent specimens are very important. Frequent and multiple biopsies, especially in extended or multiple lesions, should be carried out. We have presented data regarding the histological changes between the first OVC and subsequent W-SCC in five patients; however, in at least one patient, the case could be considered an example of coexisting OVC and W-SCC.

It is also notable that one of our patients showed true anaplastic transformation to spindle cell carcinoma. This finding was ascertained by immunohistochemical study, using epithelial membrane antigen, vimentin, and keratin.

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