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Review Article

Is primary radiotherapy an appropriate option for the treatment of verrucous carcinoma of the head and neck?

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Abstract
The literature on verrucous carcinoma of the head and neck was reviewed to analyse the use of primary radiation therapy in the treatment of this lesion. The results emphasize an overall local control rate of 43.2 per cent, and 6.7 per cent of true anaplastic transformation following irradiation. Diagnosis remains the fundamental problem: without a correct diagnosis of verrucous carcinoma, no correct treatment can be applied.

Key words: Head and neck neoplasms; Carcinoma, squamous cell

Verrucous carcinoma is a low-grade, locally aggressive variant of squamous carcinoma. This lesion was initially mentioned by Friedell and Rosenthal in 1941 as being papillary verrucoid in character, but it was first recognized and named in the oral cavity by Ackerman in 1948, who stressed that this neoplasm must not be confused with squamous carcinoma because it differs both in structural characteristics and in prognosis (which is excellent); he also added, 'If a lesion looks cytologically like carcinoma, it is not a verrucous carcinoma' (Rosai, 1996). Great confusion still exists, however, in the diagnosis and treatment of this tumour.

The present review identifies all reported cases of verrucous carcinoma of the head and neck that were treated with primary radiation therapy. Patients who failed to meet the histological criteria for the diagnosis of verrucous carcinoma were excluded and the results are summarized in Table I.

Many authors have reported lesions as verrucous carcinoma, but their histological appearance or biological behaviour was suggestive of squamous cell carcinoma (see Table II). Histological re-examination of tumours initially classified as verrucous carcinomas has revealed that about 50 per cent were well-differentiated squamous cell carcinomas with a verrucous pattern (Ryan *et al.*, 1977; Sllamniku *et al.*, 1989).

Pathologists use very different criteria in diagnosing verrucous carcinoma. Sometimes they resort to the ambiguous expression 'squamous cell carcinoma with verrucous appearance', but histological re-examination of this tumour usually supports a diagnosis of squamous cell carcinoma (conventional or papillary types) (Ferlito *et al.*, 1998). Verrucous carcinomas containing areas that are indistinguishable from conventional squamous cell carcinoma have also been reported in the literature (Batsakis *et al.*, 1982; Medina *et al.*, 1984): they are called hybrid carcinomas and are more aggressive than verrucous carcinomas. Ishiyama *et al.* (1994) suggest that these hybrid tumours are probably identical to papillary squamous cell carcinoma thus typical verrucous carcinoma should be distinguished from well-differentiated squamous cell carcinoma and from papillary squamous cell carcinoma (Ferlito *et al.*, 1998). A correct diagnosis is imperative in order to institute the most appropriate treatment and to compare results. Some of the cases previously reported in the literature as verrucous carcinomas were consequently not included in a recent review (Sllamniku *et al.*, 1989). Ever since the first report of verrucous carcinoma there has been controversy regarding the treatment of choice for this lesion in the head and neck area. In particular, there has been considerable discussion about the role of irradiation in the management of verrucous carcinoma, as it is said to be radio-resistant. This tumour has been treated in various ways. Several authors (Kraus and Perez-Mesa, 1966; Perez *et al.*, 1966; Biller *et al.*, 1971; van Nostrand and Olofsson, 1972; Ryan *et al.*, 1977; Ferlito and Recher, 1980; Myers *et al.*, 1980; Batsakis *et al.*, 1982; Sllamniku *et al.*, 1989) indicate surgery as the treatment of choice for verrucous carcinoma,

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TABLE I

VERRUCOUS CARCINOMA OF THE HEAD AND NECK: TREATMENT WITH PRIMARY RADIOTHERAPY

Author(s), Institution, Country	Year of publication, Years of interval	No. of patients	Site	Cure (%)	Failure (%)	Remarks
Goethals *et al.* Mayo Clinic, Rochester, Minn	1963 (1935–1957)	1	Oral cavity	–	1	We have not included nine patients in which the primary treatment was diathermy and radiation therapy. Six of these patients presented with recurrence.
Kraus and Perez-Mesa Barnes Hospital, St. Louis, Mo	1966 (1948–1962)	15	Oral cavity (13) Nasal fossa (2)	–	15	This series includes two previous series (Ackerman, 1948; Perez *et al.*, 1966)
McMillan Hospital, St. Louis, Mo	(1948–1962)					Anaplastic transformation: four cases (three oral cavity, one nasal fossa).
Ellis Fischel State Cancer Hospital, St. Louis, Mo	(1942–1962)					Lymph node metastases were found in four cases treated with irradiation, apparently as a result of alteration of the biological character of the lesion. Another two cases showed a recurrence, but they have been excluded because the sites of occurrence were vagina and penis.
Fonts *et al.* Tumor Clinic, University of Kentucky Medical Center, Ken	1969 (1961–1966)	4	Oral cavity	3	1	The authors reported 10 patients with verrucous carcinoma, actually only a few cases showed the histological criteria of verrucous carcinoma. In one case (*Case 9*) Anaplastic transformation was reported.
Biller *et al.* McMillan Hospital, St. Louis, Mo	1971 (1961–1970)	3	Larynx	–	3	The authors reported a series of 15 cases of laryngeal verrucous carcinoma.
Mason Withington Hospital, Manchester, England, UK	1972	1	Oral cavity	–	1	The diagnosis of verrucous carcinoma was retrospective.
Demian *et al.* Shands Teaching Hospital and Veteran Administration Hospital, Gainesville, Fla	1973 (1962–1972)	2	Oral cavity	–	2	The third reported patient who received primary radiation therapy had a lesion in the cervix uteri. Also in this case there was recurrence after irradiation.
Elliott *et al.* Vancouver General Hospital, Vancouver, Canada	1973	5	Oral cavity (3) Larynx (1) Nose (1)	3	2	The authors presented 33 cases of verrucous carcinoma, 24 of which were localized in the head and neck, but only in 10 cases of otolaryngological areas did they report clinical data.
Hyams Armed Forces Institute of Pathology, Washington, DC	1975	10	Larynx	–	10	The author reported 12 cases of verrucous squamous cell carcinoma treated with radiotherapy, but Hyams *et al.* (1988) reported that two of these cases were actually squamous cell carcinoma.
Schwade *et al.* University of California, San Francisco, Cal	1976 (since 1966)	6	Oral cavity (5) Hypopharynx (1)	5	1	One patient died nine months after irradiation from distant metastases. Smith *et al.* (1985) believed that this patient most likely had a radiation-induced transformation to an anaplastic carcinoma.
Ryan *et al.* Mayo Clinic, Rochester, Minn	1977 (1964–1974)	3	Larynx	–	3	The authors excluded 50 per cent of the lesions classified previously as VC.
Burns *et al.* Princess Margaret Hospital, Toronto, Canada	1980 (1960–1975)	11	Oral cavity	4	7	Five of these 11 patients died of their verrucous cancer at four, 11, 18, 30 and 36 months following treatment. The authors do not explain if in the patient dead within six months of completing therapy, of associated squamous cell carcinoma there was evidence of recurrent verrucous carcinoma. Probably there was, since shortly afterwards they underlined the absence of recurrent verrucous carcinoma in a patient treated with surgery and dead of associated squamous cell carcinoma.
Ferlito and Recher Department of Otolaryngology, Padua University, Padua, Italy	1980 (1966–1978)	1	Larynx	–	1	This series includes several series of previous publications (Babighian and Ferlito, 1974; Ferlito, 1975; Ferlito, 1976; Ferlito *et al.*, 1976).

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TABLE I – *continued*

Author(s), Institution, Country	Year of publication, Years of interval	No. of patients	Site	Cure (%)	Failure (%)	Remarks
McClure *et al.* Department of Otolaryngology, Toronto General Hospital, Toronto, Canada	1984 (1972–1982)	3	Oral cavity (2) Larynx (1)	2	1	Five of the 15 identified cases of VC of the head and neck were well differentiated squamous cell carcinomas with a verrucoid appearance.
Medina *et al.* Anderson Hospital, Houston, Tex	1984 (1946–1980)	12	Oral cavity	7	5	Foci of less differentiated squamous carcinoma coexisted within the larger VC in 20 per cent of the cases.
Hamlyn *et al.* Royal Marsden Hospital, London, England, UK	1986 (1949–1984)	4	Larynx	3	1	The authors reported nine cases of verrucous squamous cell carcinoma, but only six cases were considered determinate.
Edström *et al.* Sahlgren's Hospital, Göteborg, Sweden	1987 (1968–1980)	6	Larynx	4	2	Anaplastic transformation was seen in two patients after irradiation. Both the patients died of disease.
Barr *et al.* Ninewells Hospital, Dundee, Scotland, UK	1988	1	Larynx	–	1	
Niparko *et al.* University of Michigan Medical Center, Ann Arbor, Mich	1988	1	Oral cavity	–	1	This is a case of invasive squamous carcinoma within a verrucous carcinoma.
Marck and Lupin University of Alberta Hospitals, Edmonton, Canada The Cross Cancer Center of Alberta, Canada	1989 (1970–1984)	2	Larynx	1	1	
Milford and O'Flynn Charing Cross Hospital, London, England, UK	1991 (1970–1985)	7	Larynx	3	4	
Hagen *et al.* Louisiana State University Medical Center, New Orleans, La	1993 (1977–1987)	2	Larynx	1	1	Anaplastic transformation was seen in one patient after irradiation. The patient died of disease.
O'Sullivan *et al.* Princess Margaret Hospital, Toronto, Canada	1995 (1961–1990)	43	Larynx	25	18	This large series includes several papers of previous publication regarding the Princess Margaret Hospital (van Nostrand and Olofsson, 1972; Rider, 1975; Burns *et al.*, 1976; Lundgren *et al.*, 1986). Anaplastic transformation was seen in one patient, as reported by van Nostrand and Olofsson (1972), Rider (1975) and Lundgren *et al.* (1986) but not mentioned by O'Sullivan *et al.* (1995). The patient died of disease. We have not included in our review the series reported by Fliss *et al.* (1994) because eight cases have been already reported by Lundgren *et al.* (1986).
Tharp and Shidnia Indiana University, Indianapolis, Ind	1995	2	Oral cavity	1	1	
Ferlito Department of Otolaryngology, University of Padua, Padua, Italy	1997	1	Larynx	–	1	Unpublished.
McCaffrey and Lewis Mayo Clinic, Rochester, Minn	1997	2	Larynx	2	–	
Total		148		64 (43.2)	84 (56.8)	

McDonald *et al.* (1982) believed that some of the cases reported by Memula *et al.* (1980) from Ellis Fishel State Cancer Hospital may be duplicated from the series reported by Kraus and Perez-Mesa (1966).

TABLE II
UNACCEPTABLE CASES OF VERRUCOUS CARCINOMA OF THE HEAD AND NECK

Author(s)	Year	Comments
Fonts *et al.*	1969	The authors reported 10 cases of VC of the oral cavity, but only in four of these the diagnosis of VC is acceptable.
Proffitt *et al.*	1970	The authors reported that the biopsy specimen was of well-differentiated verrucous epidermoid carcinoma.
Cardo and Stratigos	1973	The authors reported one case of VC of the oral cavity, but the photomicrograph of the tumour was not consistent with a VC.
Fisher	1975	The author reported 31 cases of VC of the larynx. In five of these, there were lymph node metastases. Probably the investigator classified as VC some well-differentiated squamous cell carcinoma.
Schrader *et al.*	1987	The authors reported two cases of VC of the oral cavity and larynx with lymph node metastases. Histological diagnosis was not convincing.
Krishnan Nair *et al.*	1988	The authors reported 52 cases of VC treated with primary irradiation. The clinical course was suggestive of squamous cell carcinoma. In almost 50 per cent of these cases there was lymph node involvement.
Vidyasagar *et al.*	1992	The authors reported 107 cases of oral VC treated with primary irradiation. The clinical course was suggestive of squamous cell carcinoma. In almost 67 per cent of these cases there was lymph node enlargement.

while others propose primary radiotherapy, with surgery in reserve in the event of failure (Rider, 1975; Burns *et al.*, 1976; Bryce, 1979; Burns *et al.*, 1980; Harwood, 1982; O'Sullivan *et al.*, 1995). Lundgren *et al.* (1986) believe that verrucous carcinoma is not radio-resistant, but less sensitive to irradiation than ordinary squamous cell carcinoma.

Neck dissection is not indicated in this neoplasm, even when enlarged and tender lymph nodes are palpated, since histological examination of these nodes has revealed only an inflammatory reaction (van Nostrand and Olofsson, 1972).

In 1993, Hagen *et al.* reviewed the reported cases of verrucous carcinoma of the larynx for the outcome of radiation therapy versus surgery. Primary radiotherapy resulted in a 49 per cent cure rate and 51 per cent failure rate (84 per cent of these treatment failures showed no response). Primary surgery resulted in a 92.4 per cent cure rate with an initial failure rate of 7.6 per cent. The major contraindication for radiation appears to be the neoplasm's high rate of recurrence, suggesting that this type of tumour should be treated primarily with surgery, only using radiotherapy for patients with a surgical risk due to their clinical condition. CO_2 laser excision is indicated for Stage I (Hagen *et al.*, 1993).

Table III summarizes the recommendations of various investigators for the treatment of verrucous carcinoma of the head and neck.

From an analysis of the literature, we have collected 148 cases of verrucous carcinoma of the head and neck treated primarily with irradiation (see Table I), the majority of which exhibited a treatment failure (persistence/recurrence), the overall local control rate being 43.2 per cent (64/148). These findings would amply support the theory that radiation therapy is far less effective than surgery because verrucous carcinoma, though not radio-resistant, is less radio-sensitive than conventional squamous carcinoma.

The risk of anaplastic transformation after irradiation is now widely acknowledged, but this matter merits critical review. Biller and Bergman (1975) and Demian *et al.* (1973) found that approximately 30 per cent of cases of verrucous cancer undergo anaplastic transformation following irradiation, but the authors only considered the series in which this phenomenon was reported. The occurrence of anaplastic transformation of a verrucous carcinoma after irradiation is overestimated (Batsakis *et al.*, 1982). In 1982, McDonald *et al.* concluded that only six cases had been reported of anaplastic transformation of verrucous cancer following irradiation in head and neck areas.

We reviewed the literature on this matter and of all the 148 lesions in the head and neck region treated with irradiation, only 10 cases (6.7 per cent) of true anaplastic transformation could be found (see Table IV). The incidence of anaplastic transformation is therefore low. This biological process has also been reported in regions other than the head and neck (see Table V). We believe that it is important to stress that *all* patients with anaplastic transformation *after irradiation* died within four months and three years of follow-up; disseminated disease was found in nine of these cases.

So-called anaplastic transformation has been reported in non-irradiated patients after surgery or cryosurgery, and also in untreated verrucous carcinoma (Batsakis *et al.*, 1982; McDonald *et al.*, 1982; Strong, 1985; Luna and Tortoledo, 1988), probably due to an incorrect histological diagnosis of verrucous carcinoma. Conventional squamous carcinoma may display areas with the microscopic features of a verrucous carcinoma (Friedmann and Ferlito, 1988). There is evidence to support a biologically different process of anaplastic transformation, or dedifferentiation, in irradiated and non-irradiated patients, considering the survival in the two groups: patients with anaplastic transformation after irradiation have a dismal prognosis, whereas the outcome for the majority of non-irradiated patients with so-called anaplastic transformation is not mentioned in the literature and their prognosis is probably similar to that of squamous carcinoma.

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TABLE III

SUGGESTED THERAPY FOR VERRUCOUS CARCINOMA OF THE HEAD AND NECK BY DIFFERENT INVESTIGATORS

Author(s)	Year	Comments
Ackerman	1948	Resection seems to be the method of choice when the lesion is at all extensive.
Goethals *et al.*	1963	Surgery is the treatment of choice.
Kraus and Perez-Mesa	1966	The response to surgical excision is excellent.
Perez *et al.*	1966	The authors indicate surgical removal of the tumour with an adequate margin.
Fonts *et al.*	1969	The authors feel that surgery is the treatment of choice, in early and easily resectable lesions. Radiation therapy should be used in advanced verrucal-type lesions in which surgical resection is difficult or not feasible.
Biller *et al.*	1971	The treatment is surgical.
Mason	1972	Surgery appears to be the method of choice.
van Nostrand and Olofsson	1972	Surgical excision is the treatment of choice.
Demian *et al.*	1973	The authors said that irradiation is contra-indicated when the diagnosis of VC is firmly established.
Elliott *et al.*	1973	The authors say that cure or control of VC by irradiation is ineffective.
Thomas *et al.*	1973	The authors suggest that VC responds poorly to irradiation therefore the treatment of choice is wide local excision.
Babighian and Ferlito	1974	The elective treatment is surgery.
Bak and Erdös	1975	Surgical excision is largely preferred to radiotherapy whenever possible.
Biller and Bergman	1975	VC should be treated surgically.
Hyams	1975	The author says that VC is a surgical disease.
Rider	1975	The author indicates irradiation with surgery in reserve for failure in the treatment of VC.
Burns *et al.*	1976	Radiotherapy alone is used for those tumours sufficiently large to require a total laryngectomy, if treated surgically. Surgery alone is used on those tumours that are small enough and localized enough to be removed by 'voice conserving' partial laryngectomy procedures.
Schwade *et al.*	1976	The authors indicate that irradiation is effective as well as surgery for treatment of VC.
Lekas *et al.*	1977	Surgery is the elective treatment. Irradiation is not recommended.
Ryan *et al.*	1977	Surgery is the preferred method of treatment.
Clayton and Jordan	1978	Irradiation should be used only as the least preferred treatment.
Bryce	1979	The author indicates irradiation with surgery in reserve for failure in the treatment of VC.
Strong *et al.*	1979	The authors suggest the use of CO_2 laser in the management of VC.
Burns *et al.*	1980	The authors suggest a combination of surgery and radiotherapy for the treatment of VC.
Ferlito and Recher	1980	Elective treatment is surgery.
Myers *et al.*	1980	The best treatment is surgery alone.
McCoy and Waldron	1981	Adequate surgical appears to be the treatment of choice.
Pesavento and Recher	1981	Surgery is the elective treatment.
Batsakis *et al.*	1982	Whenever possible, surgical removal is advised over radiotherapy. This selection is based on effectiveness of control and not on the potential risk of transforming the VC into a far more biologically aggressive lesion. Planned combination therapy with pre-operative radiotherapy to reduce the size of the tumour should be evaluated.
Harwood	1982	The author advocates irradiation with surgery in reserve.
Maw *et al.*	1982	The authors indicate to treat VC by endoscopic removal reserving more extensive surgery in the case of endoscopic failure.
McDonald *et al.*	1982	There is no doubt that complete surgical excision is the treatment of choice. However, irradiation may be an effective alternative if surgical treatment is contra-indicated.
Newman *et al.*	1983	The authors suggest a combination of surgery and radiotherapy for the treatment of VC.
Blakeslee *et al.*	1984	CO_2 laser is ideal for diagnosing and treating glottic VC.
McClure *et al.*	1984	Surgery appears as the most effective form of therapy.
Medina *et al.*	1984	Surgery is the treatment of choice, although irradiation can be used to treat selective patients.
Abramson *et al.*	1985	The authors believe that radiotherapy should not be used unless the potential consequences and molecular mechanisms are fully explained.
Colman *et al.*	1985	The preferred treatment is wide local excision. Radiation therapy appears to be contra-indicated.
Smith *et al.*	1985	The authors do not recommend radiotherapy.
Hamlyn *et al.*	1986	VC should be treated like other squamous carcinomas.
Lundgren *et al.*	1986	Lesions that can not be managed endoscopically can often be treated by cordectomy or partial laryngectomy, saving radiotherapy for those extensive lesions that require a total laryngectomy for complete removal of the tumour. VC, although not radio-resistant, seems less radiosensitive than ordinary squamous cell carcinoma.
Edström *et al.*	1987	The authors provide evidence of increased metastatic potential after irradiation for T1–2 VC as compared with the common type of squamous carcinoma.
Barr *et al.*	1988	
Lee	1988	The author suggests endoscopic removal of the lesion reserving surgery and irradiation for the more refractory cases or those in which endoscopic removal is incomplete.
Niparko *et al.*	1988	The treatment of choice for VC of the oral cavity is wide local excision without regional neck dissection.
Marck and Lupin	1989	Although evidence for degeneration of VC into an anaplastic carcinoma remains inconclusive, surgery is the best treatment.
Sllamniku *et al.*	1989	The authors say that irradiation may have some clinical validity as a therapeutic alternative if surgical treatment is contra-indicated.
Milford and O'Flynn	1991	The authors believe that endoscopic laser excision may be a reasonable alternative to more radical surgery in this highly differentiated neoplasm.
Rink	1991	The author reports that adequate surgical excision is considered the treatment of choice.
Hagen *et al.*	1993	The authors recommend laser excision for T1 lesions and surgical excision for T2 to T4 lesions. Primary irradiation is ineffective in half of the cases.
O'Sullivan *et al.*	1995	The author indicates irradiation with surgery in reserve for failure in the treatment of VC.
Tharp and Shidnia	1995	The authors found that the rate of local control with primary irradiation is less than 50 per cent, however recommend primary irradiation with surgical salvage in the case of large lesions.
Maurizi *et al.*	1996	Surgery seems to be the most effective treatment.

TABLE IV

ANAPLASTIC TRANSFORMATION *AFTER IRRADIATION* IN VERRUCOUS CARCINOMA OF THE HEAD AND NECK

Author(s)	Year	Site	No. of cases	Comments
Kraus and Perez-Mesa	1966	Oral cavity Nasal fossa	4	All these patients died < 1 year of follow-up with metastases (disseminate disease in two patients). This series includes three cases of anaplastic transformation reported by Perez *et al.* (1966).
Fonts *et al.*	1969	Oral cavity	1	The patient died a few months later (< 1 year of follow-up), after the failure of chemotherapy.
van Nostrand and Olofsson	1972	Larynx	1	The patient died 10 months after radiotherapy with a clinical diagnosis of disseminated malignancy.
Smith *et al.*	1985	Larynx	1	The patient died within four months with determinate disease.
Edström *et al.*	1987	Larynx	2	One patient died three years after irradiation with mediastinal lymph node metastases with periglandular growth, while the other patient died two years after radiotherapy with regional metastases.
Hagen *et al.*	1993	Larynx	1	The patient died with disseminate disease five months after the irradiation.

TABLE V

ANAPLASTIC TRANSFORMATION AFTER RADIOTHERAPY IN VERRUCOUS CARCINOMA IN *NON* HEAD AND NECK AREA

Author(s)	Year	Site	No. of patients
Gallousis	1972	Vulva	1
Bardini *et al.*	1980	Oesophagus	2
Väyrynen *et al.*	1981	Vulva	1
Fukunaga *et al.*	1994	Penis	1

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