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Continuous Hyperfractionated Accelerated Radiotherapy in the Treatment of Carcinoma of the Columella and Vestibule of the Nose

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Twenty-one patients with squamous cell carcinoma of the nasal columella and vestibule were treated at the Mount Vernon Centre for Cancer Treatment between March 1986 and January 1994. Tumours ranged from 15 to 55 mm in maximum dimension (median 25 mm). All patients were treated with radical intent with continuous hyperfractionated accelerated radiotherapy (CHART). This group was analysed with respect to tumour control, tumour cell kinetics and radiation-induced morbidity at a median time to last follow-up of 40 months. Particular attention was paid to the detailed evaluation of late radiation changes. Patients who were still alive were assessed as to the satisfaction with the cosmesis of their treated nose. Four patients had relapse of disease either at the primary site alone (2), in neck nodes (1) or in both regions (1). One patient was successfully salvaged with surgery. Cell kinetic studies showed that cancers at this site may have potential for rapid cellular repopulation similar to cancers developing at other head and neck sites. CHART was well tolerated by patients. Late skin changes were remarkedly slight (despite full skin dose) and overall cosmesis excellent with this radiotherapy schedule.

Keywords: cell kinetics, CHART, columella, cosmesis, nasal vestibule, radiotherapy, squamous cell carcinoma

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INTRODUCTION

CARCINOMAS of the nasal columella and vestibule are relatively rare. However, the management of these tumours poses a challenge in terms of maintaining good cosmesis and nasal function. In addition, they can follow an aggressive local course despite an often deceptively trivial appearance. Radical surgery at this site often results in marked deformity and, thus, the policy at Mount Vernon Hospital, like other centres [1–4], has been to treat these tumours primarily with radiotherapy, reserving surgery for salvage of relapse. Inevitably, reports dealing with the management of nasal vestibule and columella carcinomas include a limited number of cases which have been accrued over long periods of time. Consequently, many series comprise patients treated with a number of different radiotherapeutic and surgical techniques, making interpretation of results difficult. Since 1986, 21 patients with cancers of the columella and nasal vestibule have been treated with radical intent at Mount Vernon Hospital with continuous hyperfractionated accelerated radiotherapy (CHART) employing a uniform radiotherapy regimen. The results of treatment are presented.

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MATERIALS AND METHODS

Between March 1986 and January 1994, 21 patients with previously untreated squamous cell carcinoma of the columella and nasal vestibule were referred to the Mount Vernon Centre for Cancer Treatment and all were deemed suitable for radical treatment. Case records were reviewed retrospectively in conjunction with pre- and post-treatment colour photographs to collect information on patients' histories (including smoking and occupational history), pathological features, treatment technique, early and late radiation-induced morbidity and outcome.

In addition, patients alive at the time of analysis in November 1994 were asked to attend the clinic for review at which time late tissue morbidity was assessed as objectively as possible by two investigators. Data on all cases were available for analysis of local control, survival and for early and late radiation morbidity. The median follow-up of patients to death or last contact was 40 months (range 5–105 months).

All but one patient underwent an MRI scan of the head and neck region to assist in the assessment of tumour extent at presentation and to help detect any nodal metastases. Wher-

ever possible, with the patient's consent, tumour cell kinetics were determined by further tumour biopsy.

All 21 patients were treated with CHART; three fractions were given daily over 12 consecutive days to a total tumour dose of 50.4 Gy in the first case and 54.0 Gy in the other 20 patients. In the first 11 patients, this dose was prescribed as a minimum tumour dose and following this (since 1990) the interaction dose was used as the point of prescription. The target volume included the primary tumour with a margin of 1.5 cm. In the majority of patients, radiotherapy was delivered through a pair of parallel opposed lateral (10) or anterior oblique (8) portals. Three patients with advanced lesions were treated with a three-field technique, employing an anterior field and two direct or oblique lateral fields to encompass the tumour volume. In all cases full skin doses were achieved with wax bolus over the whole field during the entire treatment period. No patients received prophylactic treatment of neck nodes.

RESULTS

Patients

15 patients were male and 6 were female. The median age of patients at presentation was 74 years, with a range of 40–83 years. The occupational histories of patients were varied but there were four engineers, two civil servants/government officers and two carpenters, one of whom had also been exposed to tar for 30 years as a road surfacer. Occupational histories for the whole group are shown in Table 1.

All but one patient had a history of cigarette smoking and all but 3 were still smoking at the time of diagnosis. Amongst 18 patients in whom a detailed smoking history was obtainable, the median of the maximum number of cigarettes regularly smoked by each patient was 20 per day (range 6–60/day). The median duration of smoking prior to diagnosis was 58 years (range 41–72 years).

Tumour characteristics

The clinical and pathological features of all 21 tumours are shown in Table 2. Tumour size was often difficult to assess accurately due to ill-defined and often deep infiltration of tissues in and around the nose. In 20 patients, the cancer had clearly arisen from the columella with or without involvement of other portions of the vestibule. Invasion of structures beyond the columella and nasal vestibule was common, in particular the "moustache" areas (the region between the nose and the vermillion lip) and the nasal septum. No patients had palpable nodal disease or lymphadenopathy on MR imaging at presentation.

Table 1. Occupational history in patients with carcinoma of the columella

Occupation	Number of patients
Engineer	4
Civil servant/government officer	2
Carpenter*	2
Print worker	1
Bricklayer	1
Farm worker	1
Welder	1
Accountant	1
Professional driver	1
Policeman	1
Painter/decorator	1
Housewife/unrecorded	5

*One patient had also worked as a road builder with exposure to tar.

Table 2. Tumour characteristics (n = 21)

Maximum dimension (mm)	< 20	6
	20–40	12
	> 40	3
Pathological grade (differentiation)	Well	6
	Moderate	7
	Poor	8
Apparent origin of tumour	Primarily columella	20
	Vestibule alone	1
Structures involved beyond columella and vestibule	None	7
	Nasal septum	10
	"Moustache" area	9
	Buccoalveolar sulcus/ alveolus	5
	Ethmoid sinuses	1

Table 3. Cell kinetics of carcinoma of the columella compared with those found in a range of head and neck cancer squamous carcinomas, all treated with CHART

	Columella ($n = 13$)		All sites ($n = 115$)
	Median	Range	Median
DNA index (% aneuploid)	46		49
Labelling index (LI) (%)	4.9	1.1–11.8	7.5
Duration of S phase (Ts) (h)	10.4	6.6–16.8	10.0
Potential cell doubling time (Tpot) (days)	7.9	2.8–27.0	4.4
Histological LI (%)	11.3	1.8–29.1	15.0
Histological Tpot (days)	3.5	1.0–18.0	2.5

Cell kinetics of 13 tumours were studied by flow cytometry after intravenous administration of 200 mg of bromodeoxyuridine (BrdUrd) prior to biopsy which was performed 4–6 h later [5]. As with squamous carcinomas at other head and neck sites, there was a considerable range of kinetic parameters. There was, however, a trend towards lower labelling indices and, therefore, lower potential cell doubling times, when the results for columella carcinomas were compared to those obtained for other head and neck sites. (Table 3). Histological studies showed, as in all other sites, areas of much higher labelling. The median value of the average labelling indices determined histologically was not significantly below the median value for all head and neck sites [6].

Radiotherapy and radiation-induced morbidity

All patients tolerated CHART with no treatment interruptions. For presentation of data, the field size was approximated by the area of one of the lateral or anterior oblique portals for

patients treated with a wedged pair of fields. The median field area over the whole group of patients was 36 cm^2, range 20–90 cm^2.

There was a confluent fibrinous reaction in the irradiated mucous membrane which presented 13–15 days after commencing treatment, as has been previously described for patients treated with CHART for tumours at other head and neck sites [7]. The mucosal reaction was limited to the upper alveolar buccal sulcus below the columella and a portion of the hard palate was included in order to obtain an adequate margin around the tumour. The mucositis was rarely troublesome and settled within 10–14 days. In only one patient, who was also suffering from early senile dementia, did the intraoral reaction significantly interfere with eating.

Despite full skin "build-up" in all cases, acute skin reactions were notably less than expected. Reactions presented at 18–21 days from the commencement of CHART and settled rapidly after 28 days. The maximum degree of erythema was graded as slight in 1 patient, moderate in 9, and marked in 11 patients. Dry desquamation was seen in 18 patients but in 10, this was limited to less than 50% of the irradiated skin, while more extensive dry desquamation was seen in 8 patients. Moist desquamation occurred in 10 patients and was usually restricted to small areas of skin around the ala nasi. Only 2 patients had moist desquamation involving more than 30% of the treated skin including the surface of the actual tumour.

Careful observations and recording of skin changes including regular follow-up colour photographs allowed for a detailed and reliable assessment of late skin morbidity in all patients. The grading system used [8] has been previously employed to report skin morbidity from CHART [7]. The absence of all but minimal late radiation skin changes in this group of patients receiving full skin doses is striking. Only 2 patients had any discoloration (one had slight erythema; the other slight pallor) within the treated area. No patients had increased pigmentation in the irradiated skin. In an elderly population the assessment of telangiectasia is always difficult and it is uncertain whether any telangiectasia seen were attributable to radiotherapy. However, 7 patients had telangiectasia over and above "baseline" skin outside the treatment area and in all cases this represented a "slight" increase (i.e. <1 telangiectatic vessel/cm^2). Only 2 patients had any evidence of late tissue oedema or subcutaneous fibrosis. In one of these the area of abnormality was limited to the lower nasal septum and in both of these the degree was scored as "slight". Women were excluded from detailed evaluation of hair regrowth although in 2 of the 6 women there was evidence of regrowth of tiny nostril hairs from treated skin. 11 of the 15 men had regrowth of facial hair within the irradiated area and in 2 of these, hair growth over the entire moustache area returned to the pretreatment level (Fig. 1).

Inconsequential mucosal telangiectasia were seen over the hard palate with late follow-up in 3 patients. Information on nose bleeds as a possible cause of late radiation-induced morbidity was available in 14 patients. 6 patients felt that they had more nose bleeds than prior to their treatment but these were precipitated only by vigorous blowing of the nose. The remainder had either no nose bleeds (7) or the same number as before (1). No patient developed nasal obstruction.

10 patients were able to participate in a personal assessment of cosmesis following treatment using a Linear Analogue Self Assessment (LASA) scale. Patients were asked to score their satisfaction with the appearance of their noses on a continuous

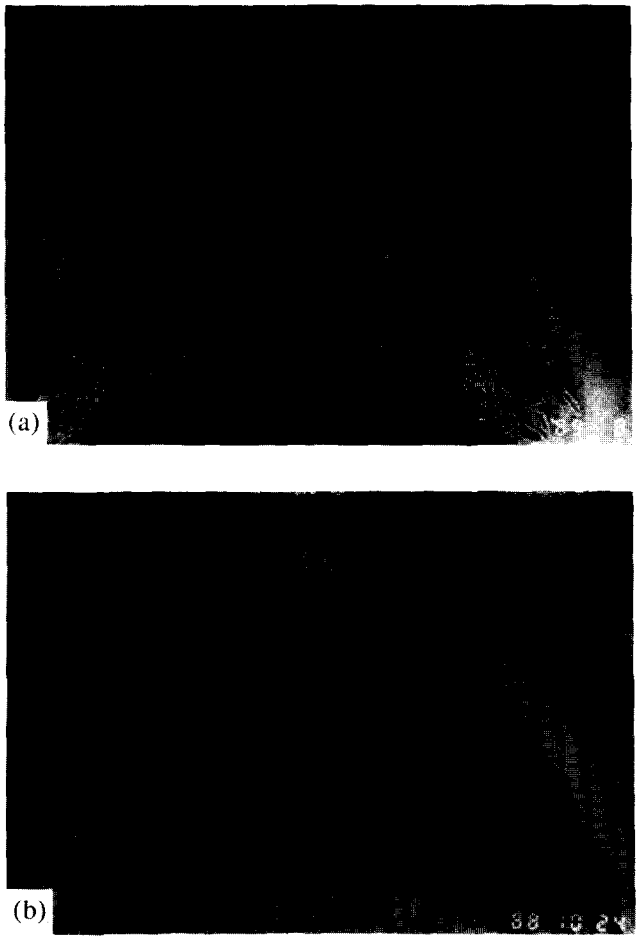

Fig. 1. Appearance of nose (a) before and (b) 39 months after CHART for a carcinoma of the columella (note: hair regrowth).

scale (from extremely poor to excellent) both prior to developing their tumour and at the current clinic visit at variable time intervals following CHART. The difference in these two measurements was used to evaluate satisfaction with cosmesis. Although patients varied in how much they liked the appearance of their noses at both points in time, without exception, all patients indicated an equal satisfaction with the appearance before and after treatment.

One patient with a very extensive tumour developed bilateral blindness due to inclusion of the optic nerves and chiasma within the radiation field and later went on to develop temporal lobe radionecrosis manifested by fitting. This was fully controlled by anticonvulsant therapy. The condition of this elderly man subsequently declined due to multiple causes including his past radiation problems and he died 3.5 years after treatment.

Outcome following CHART

Twenty of 21 tumours showed complete tumour regression with a median time to regression of 38 days (range 15 days–11.5 weeks). The patient failing to achieve a complete response developed nodal disease 4 months after the initiation of radiotherapy and despite salvage surgery to the primary and neck disease, relapsed again at the primary site and in the opposite neck before dying of his disease 10 months after initial treatment. One patient relapsed at the primary site at 3 months

and was successfully salvaged with a partial rhinectomy, remaining free of disease at 6.5 years. A 75-year-old woman (incidentally, the only non-smoker) developed bilateral nodal disease 2 years and 9 months after treatment and received a second course of CHART to the submandibular region following bilateral suprahyoid neck dissections. She deteriorated rapidly and died soon after the completion of treatment. Post-mortem revealed lung metastases and no evidence of local recurrence. A 71-year-old woman failed at the primary site at 3 months. In view of her general frailty and senile dementia, no salvage treatment was possible and she died of her disease at 5 months. No other patients developed distant metastases.

The overall actuarial recurrence-free survival and local control rates of this group of patients with cancers of the nasal columella and vestibule treated with CHART and salvage surgery are 81% and 86%, respectively, at 3 years. There have been six deaths from intercurrent causes, including three from second cancers (two from non-small cell lung cancer; one from carcinoma of head of pancreas). There was one death from ischaemic heart disease. A primary cancer of the larynx was subsequently diagnosed in an 80-year-old man and treated with CHART; this patient died of a ruptured abdominal aortic aneurysm, free of cancer at both sites, 22 months from the start of his first course of CHART. The exact cause of death in the last patient is unknown although cerebral radionecrosis was contributory; the patient was free of disease at the time of death.

DISCUSSION

The results of CHART in the treatment of carcinomas of the columella and vestibule are at least comparable, in terms of local control and disease-specific survival, to the best reported literature figures using surgery and/or external beam or interstitial radiotherapy [2, 4, 9–11]. There was no selection of cases in this series, which includes large and locally aggressive cancers. However, it is of interest that the patients who had local recurrence were not those that had the largest tumours. Proponents of interstitial implantation for these tumours report good local control rates [12–14] but generally agree that larger lesions are rarely suitable for treatment by implantation alone. It is difficult to make a meaningful comparison with previously treated tumours or those in other series, as only limited matching is possible due to inevitable imprecision in data concerning size and extent of tumour.

This series supports the evidence in the literature that smoking is an important aetiological factor in carcinoma of the nasal columella and vestibule [14, 15]. Exposure to UV light may be less important in the causation of cancer at this site than at other skin head and neck sites in view of the relative protection of this area and indeed, in this series we found a preponderance of indoor occupations amongst our patients.

Few studies specifically describe the exact site of origin of tumours around the nasal vestibule region and often the columella is not mentioned as a separate site. Only one of the tumours which we have reported was clearly not of origin in the columella. We suspect that this site is perhaps more common relative to true vestibule cancers than has previously been reported. The situation is further complicated in the literature by the inclusion of cancers of the true skin of the nose in some series [12].

A noteworthy finding of this study is the remarkable skin recovery following an accelerated radiotherapy regime, despite full skin dose. At no other site than the nose could this result be more fortuitous, where, as many authors have previously stressed [3, 11, 16], a near-normal appearance is one of the main goals of treatment. Other studies [4, 17] have also reported good cosmesis with conventional external beam radiotherapy. However, a detailed assessment of skin colour, texture and telangiectasia is not reported and in particular, hair regrowth has not been recorded. This suggests that long-term skin changes resulting from doses required to control squamous cell carcinoma given in 1.5 Gy per fraction are less than those associated with 1.8–2 Gy (or larger) fractions delivered in a conventional course of radiotherapy. This absence of major or even moderate morbidity compared with a 9% significant late complication rate reported in the Princess Margaret Hospital series of 56 patients with carcinomas of the nasal vestibule [2]. Mendenhall *et al.* [18] describe in their series of 13 patients treated with radium needle implants and/or external beam radiotherapy at the University of Florida, 2 patients who had recurrent skin ulceration and 2 others who developed nasal cavity strictures requiring dilatation.

Most important in the assessment of cosmesis is the patients' satisfaction with the overall appearance of the nose. In the current study, the near-normality of tissues determined on clinical assessment of skin changes by the doctor has been borne out by patients' self-assessment of appearance following treatment. It is worth noting that virtual absence of late skin damage was universal following treatment of the largest to the smallest tumours in this series and similarly (the two are clearly related) there did not appear to be any increase in late skin radiation effects even for the largest fields (up to lateral field area sizes of 90 cm^2). The good cosmesis seen with brachytherapy [12, 14, 19] on the other hand, is achieved only when tumoricidal doses are delivered to relatively small volumes.

CHART is unsuitable for those cases with extensive disease where the target volume must include the optic chiasma and/or brain because of the incidence of radiation morbidity in these structures. This is considered to be due to a long half-time of repair of sublethal damage in the central nervous system and the inadequacy of a 6 h interfraction interval for this process to near completion [20].

As in this group of patients, the experience of other investigators is that loco-regional recurrence of columella and nasal vestibule tumours usually occurs within 6 months of treatment and is unusual beyond 18 months [9, 21]. However, late recurrence in lymph nodes was observed beyond 2.5 years in 1 patient who died of lung metastases. The rate of intercurrent deaths in this series is high, reflecting the age and smoking histories of the patients.

One patient in the present series developed a neck node recurrence in the presence of persistent disease at the primary site. This patient died of disease following further nodal and primary recurrence after extensive surgery to the nose and neck. The other patient developing nodal disease had no evidence of relapse in the nose but died with lung metastases and probable sepsis soon after attempted salvage with surgery and radiotherapy. Other authors have noted that patients with failure in neck nodes have overall a much poorer prognosis [3, 22]. In spite of this, the rarity of node-only recurrences (which are more readily salvaged with surgery) leads many authors to support the policy of withholding prophylactic nodal treatment but continuing close follow-up of the neck [2, 18].

Salvage surgery was attempted in 3 patients in this series.

One tumour recurred locally and in the neck following surgery to both regions, 1 patient died immediately following the salvage attempt and the other was successfully salvaged by partial rhinectomy. Vendelbo Johansen *et al.* [1] found that surgery successfully salvaged recurrence of nasal vestibule and columella tumours following radiotherapy in 12 of 22 cases. Weinberger *et al.* [11] reported a curative surgical salvage rate of 7 of 12 patients. Mendenhall *et al.* [18] make the important point that *provided* meticulous and frequent follow-up is undertaken, salvage procedures following radiotherapy rarely require more tissue to be removed than would have needed to be excised if an initial surgical approach had been adopted. This supports the policy of initial radiotherapy with surgery reserved for failure.

Stanley's [23] 20 year experience with rhinectomy for malignant disease (as either primary or salvage treatment) was that 40% of patient with squamous carcinoma died of cancer, usually with uncontrolled local disease and that the results of surgical reconstruction were unsatisfactory from a cosmetic point of view. Expertise in surgical reconstruction is advancing but improvement in prosthetic technology has been a major contribution to acceptable facial appearance following surgery in more recently treated cases.

The degree of cellular differentiation of these tumours as determined by standard histological grading did not appear to relate to tumour control, as seen in this small series. The kinetic data obtained for those tumours which failed, similarly, did not differ from those where there was continued success. The short cell doubling time, particularly that determined using a labelling index derived from histological study, suggests that columellar cancers, like other squamous carcinomas in the head and neck region, have a potential for rapid cellular repopulation. This gives support for the use of an accelerated regime of radiotherapy such as CHART [24].

Radiotherapy remains the treatment of choice for carcinomas of the columella and nasal vestibule. As a schedule of radiotherapy, CHART is applicable to all tumours at this site ranging from small to extensive, is well tolerated by and very acceptable to an elderly group of patients, achieves very good local control and disease-free survival rates, and attains excellent long-term skin recovery and consequent cosmesis.

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