Key points:

1. Most patients (82%) present with locally advanced disease
2. Most patients (90%) have a smoking history, over one third have poor PS and all have co-morbidities (58% single, 42% multiple)
3. 7% of patients were unsuitable for investigations to obtain a histological diagnosis, nearly half of patients were unsuitable for anti-cancer treatment
4. In those treated radically, the pattern of treatment failure is loco-regional
5. Multi-modality treatment with surgery and RT appears to confer a survival advantage in patients with stage 4a/b disease

Survival outcomes in Hypopharyngeal cancer in the West of Scotland Cancer Network

Introduction

Approximately 5% [1] of all mucosal head and neck (H&N) squamous cell cancers (SCC) arise from the hypopharynx. [1] Patients with hypopharyngeal SCC (HPSCC) tend to have a poor prognosis compared with other subsites with reported 5-year survival of 27% in the UK.[2] Most patients (80%) have stage III/IV disease at presentation.[3]

There are very few HPSCC-specific studies and this subsite is not well represented in more general H&N SCC trials. Thus, deciding the best treatment plan is difficult and relies on the expertise of an experienced multi-disciplinary team (MDT).[4]

Patient fitness for treatment complicates matters further. The incidence of H&N cancer increases with age and is closely correlated with deprivation[1] and the associated disproportionate burden of smoking, alcohol use and ill health.

The aim of this series was to review outcomes of patients with HPSCC in our cancer network.

Materials and methods

This retrospective study included all patients with a histological or radiological diagnosis of HPSCC made from August 2016 to August 2018. They were identified from the cancer network database. Subsites included pyriform fossa, post cricoid and posterior pharyngeal wall.

Data including patient demographics, treatment details and outcomes were extracted from case records.

Ethics statement

Patient data were used to evaluate standard of care treatment and reviewed only by members of the responsible clinical team, in compliance with data protection regulations. Approval for the project was given by the Caldicott guardian for each health board in the managed clinical network (MCN).

Diagnosis and Staging

In suitable patients, examination under anaesthetic (EUA) and biopsy of the primary site was carried out to allow clinical staging and histological diagnosis. A radiological diagnosis was made when the patient was unsuitable for histological confirmation and was confirmed by the MDT. Every patient underwent cross-sectional imaging with a contrast enhanced CT scan of head, neck, chest and upper abdomen. FDG PET-CT was undertaken on a case by case basis, generally for those with advanced disease, or with suspicion of distant metastases. Each case was discussed at the regional MDT meeting to confirm staging (American Joint Committee on Cancer: 7th edition Cancer Staging (AJCC) 7th edition) and recommend treatment.

Primary surgery

Surgical approaches included resection of primary site only, or with unilateral, bilateral or central neck compartment dissection. All were open surgery, with flap reconstruction as appropriate.

Adjuvant radiotherapy (RT) was recommended for established pathological risk factors, especially in the presence of several features (pT3-4, pN1-3, vascular/lymphatic/perineural invasion, close (1-5mm) mucosal resection margins). Those with involved margins (<1mm) or extranodal extension (ENE) were also considered for concurrent chemoradiotherapy (CRT) if eligible for platinum-based chemotherapy.

Radiotherapy/chemoradiotherapy

All patients underwent RT with Volumetric Arc Modulated Therapy (VMAT). Patients receiving RT as primary treatment received 65Gy/30# to areas of gross disease and involved nodal levels and 54Gy/30# to areas at risk of microscopic disease as per international

guidelines.[5] Post-operative RT was 60Gy/30# to the surgical bed and involved nodal levels, and 54Gy/30# elective dose. Patients with ENE or involved margins received 65Gy/30# to these high risk areas. Consensus for RT target volumes was achieved through consultant-led team peer-review. Concurrent chemotherapy was cisplatin 100mg/m2 on day 1 and 22 of RT for those eligible.

Systemic anti-cancer therapy (SACT) alone

Chemotherapy alone was administered in the induction and 1st line palliative settings. Regimens included carboplatin AUC 5 and paclitaxel 175mg/m2 day 1, q21 and carboplatin AUC 5 day 1/5FU 750mg/m2/day 1-4, q21 for up to 6 cycles. Nivolumab, an anti-PD1 antibody, was used in the 2nd line palliative setting, 240mg every 2 weeks for up to 2 years.

Best supportive care (BSC)

Supportive and symptom control was used in cases where patients were considered unsuitable for anti-cancer treatment, disease was so advanced to render treatment futile or if this was a patient's preference.

Palliative radiotherapy

Short courses of palliative RT (one to five fractions) were administered alongside palliative SACT and BSC as indicated.

Statistical Analysis

Follow-up and survival statistics were calculated from the diagnosis until death or date of censor. The date of censor was the date the survival status of patients was last recorded. This varied from October 2019 to February 2020. One and 2-year rates with 95% confidence intervals for overall survival (OS) were estimated using the Kaplan-Meier method. The log-rank test was used to detect differences in survival by age group, performance status and stage.

Results

Patient and disease characteristics

118 patients were evaluable. 8 (6.7%) patients had a radiological diagnosis, the remainder were biopsy proven HPSCC. Patient and tumour characteristics are presented in Table 1.

Characteristics			Number (%)
Sex		Male:Female	93 (78.8): 25 (21.2)
Age (years)		Mean (range)	66.2 (41.0-97.8)
		<70	76 (64.4)
		70+	42 (35.6)
Performance Status (ECOG)		0	35 (29.6)
		1	44 (37.3)
		2+	39 (33.1)
Smoking history		Former/current	106 (90)
		No	12 (10.0)
Co-morbidities		Single	69 (58)
		Multiple	49 (42)
		Previous cancer diagnosis	31(26.3)
		Previous head & neck cancer	19 (16)
Staging (AJCC 7th edition)	T stage	1-2	16 (13.5)
		3-4	102 (86.5)
	N stage	0	43 (36.4)
		1	18 (15.3)
		2-3	57 (48.3)

Table 1: Patient demographics and staging

Treatments and outcomes

Table 2 shows the treatment modalities delivered and outcomes, stratified by stage of disease. The median potential follow-up was 2 years. The probability of survival at 24 months was higher in patients of good performance status (PS 0-1: 41.7%, 95% CI 29.7-53.2% Vs. PS ≥2: 27.5%, 95% CI 13.9-43.0%; log-rank test p=0.006). Patients aged 70 years or over had a lower probability of survival at 24 months compared to those under 70 (<70yrs 44.5%, 95% CI 27.1 – 55.9% Vs ≥70yrs 24.4%, 95% CI 12.6 – 38.3; log-rank test p=0.011). 57 (48.3%) of the 118 patients were treated with radical intent, of which 19 (33%) died at time of follow-up. 14 of these deaths were cancer related and 5 were from other causes. The median time from primary surgery to adjuvant RT was 17 weeks. Survival varied by stage (log-rank test p<0.0001).

Stage (number)	% Overall Survival at 24 months (95% CI)	Disease recurrence in those treated radically (number)		Treatment modality (number)	% Overall Survival at 24 months (95% CI)
		Loco-regional only	Distal +/- locoregional		
Stage 1-2 n=16	67.5 (38.3 – 85.1)	2/12	1/12	Surgery (n=2)	100
				Surgery +adjuvant RT (n=1)	100
				RT alone (n=9)	64.8 (25.3-87.2)
				BSC (n=4)	50.0 (5.8-84.5)
Stage 3 N=15	58.3 (29.3 – 78.9)	3/12	0/12	Surgery (n=2)	0
				Surgery +adjuvant RT	100

				(n=1)	
				CRT (n=6)	83.3 (27.3-97.5)
				RT alone (n=3)	0.0
				BSC (n=3)	0
Stage 4 N=87	27.3 (17.8 – 39.0)	5/33	2/33	Surgery (n=12)	50.0 (20.8 to 73.6)
				Surgery +adjuvant (n=7)	100.0
				CRT (n=5)	0.0
				RT alone (n=9)	53.3 (12.5 to 82.7)
				Palliative chemotherapy (n=5)	40.0 (5.2 to 75.3)
				BSC (n=49)	7.7 (2.0 to 18.4)

Table 2: Treatment modalities and outcomes

Stage 1 and 2

There were 16 patients (13.6% of whole cohort) with early stage disease. The median OS was not reached. Of the 3 patients who had primary surgery, adjuvant RT was indicated for 1 patient due to close margins. 4 of 16 patients with early stage patients were not suitable for curative treatment due to poor PS and co-morbidities.

Stage 3

Fifteen patients (12.7%) had stage 3 disease. The estimated median OS was 27 months.

Stage 4a/b

The majority of the cohort had stage 4a or 4b disease – 82 patients (69.5%). Despite 19 patients undergoing primary surgery, adjuvant RT was delivered in only 7 (36.8%). Reasons for no adjuvant RT were patient choice, fitness and early disease recurrence. The estimated median OS for stage 4a patients was 12 months and for stage 4b patients was 7 months.

Stage 4c

The 5 patients who had stage 4c HPSCC were all managed with best supportive care. The median OS was 3 months for these patients.

Discussion

This is the first UK series evaluating only HPSCC in a contemporary H&N cancer practice. It illustrates that the majority of patients present with locally advanced disease and survival remains poor despite advances in diagnosis and treatment. Nearly half of our patients were managed with BSC only. While this was highest in the advanced disease setting, 4 out of 16 patients with early stage disease were not suitable for active treatment. This demonstrates the challenges encountered in delivering even single modality treatment to this group.

Comparisons to other studies

Of patients who were suitable for active treatment, single modality surgery or RT appear to have equivalent outcomes in early stage disease. Patients with stage 3 disease may be optimally treated with combined modality therapy, either surgery plus adjuvant RT or primary CRT. This is in keeping with data from Tsai et al [6] where OS rates in the primary surgery and CRT groups were similar. For patients with stage 4a/b disease highest survival was achieved for combined modality therapy of surgery and adjuvant RT, again this is in keeping with earlier publications.[6,7] However, prior to embarking on this course, the

likelihood of the patient being able to complete multi-modality treatment in a timely fashion must be considered.[8] Our data demonstrates this is feasible in the minority.

For patients treated radically the most common site of recurrence was loco-regional. The recently published UK Phase III ART-DECO study also found this to be the case.[9] This trial examined dose escalated intensity-modulated radiotherapy (IMRT) in patients with locally advanced laryngeal and hypopharyngeal cancers, finding it did not improve locoregional control (LRC) compared to standard of care. Improved LRC remains therefore an unmet need in locally advanced HPSCC.

Limitations

Given the retrospective nature of our own and previous work it remains uncertain whether selection bias contributes to the apparent survival benefit seen with multi-modality therapy including primary surgery. This limitation and the lack of toxicity and patient quality of life data is acknowledged along with our modest numbers. However, our cohort of this rare SCC were captured over a short time period, meaning approaches to diagnosis and treatment are homogeneous and reflective of contemporary practice.

Conclusions

Most patients with HPSCC present with locally advanced disease and are unsuitable for active anti-cancer treatment. For those treated radically the pattern of treatment failure is loco-regional. A multimodality approach for locally advanced disease with surgery and radiotherapy appears to be advantageous in terms of survival.

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