
TRIPLE THERAPY FOR ADVANCED SQUAMOUS CELL CANCER OF THE HEAD AND NECK

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This study presents the results of treatment for Stage III and IV squamous cell carcinoma of the head and neck at the Princess Alexandra Hospital and Queensland Radium Institute, Brisbane. Patients were treated using a programme of sequential chemotherapy, surgery and radiotherapy. Between 1980 and 1988, 116 patients commenced the programme and 85 completed the treatment as planned.

The Price-Hill regimen of chemotherapy was used until 1986 after which time it was replaced by cisplatin/5-fluorouracil (5FU). Two courses were usually given achieving an overall response rate of 36% (12% complete response). Cisplatin/5FU produced an overall response rate of 56% compared with 24% for the Price-Hill regimen. Radical surgical resections were performed using a free flap reconstruction in the majority of patients. Radiotherapy fields usually covered the primary site and both cervical lymph node areas to a dose of 50–60 Gy in 5–6 weeks.

The lengthy treatment was generally well tolerated although there were two chemotherapy and two peri-operative deaths. The overall actuarial survival for the 85 patients completing the triple therapy was 60%. These patients were analysed in more detail for possible prognostic factors.

Key words: chemotherapy, free flap reconstruction, head and neck cancer, radiotherapy.

Introduction

The management of advanced head and neck cancer continues to be a challenge with overall 5 year survival rates showing little improvement over the past decade.1 The use of combined surgery and radiotherapy however, has been shown to improve not only overall survival but also reduce the rate of locoregional recurrence.2 This improvement in survival and local control, although not increasing the incidence of distant metastasis, has caused them to become a major cause of morbidity and mortality in those patients who survive.3

The difficulties in management of patients with Stage III or IV disease have been addressed by this Unit with the adoption of combined modality treatment which started in 1980. Since that time, where possible, the recommended treatment for patients with advanced disease has been two courses of pre-operative chemotherapy followed by surgery and radical postoperative external beam radiotherapy.

The results of this combined modality treatment which was used on 85 patients at the Princess Alexandra Hospital, Brisbane over a period of 8 years 1980–88 are reported here.

Methods

Patients with previously untreated squamous cell carcinoma of the head and neck were eligible to enter the treatment regimen. The diagnosis was proven histologically and each case was staged using the UICC classification. Patients were then seen at the Head and Neck clinic; this is a multidisciplinary clinic comprising ear, nose and throat, general, plastic and oral surgeons, plus medical oncologists, radiation oncologists, speech therapists and social workers, all of whom contribute to the patients' final treatment plan. Patients had to have no evidence of distant disease, normal renal function and be fit enough for a general anaesthetic. This meant that patients who were particularly frail and spending more than 50% of their time in bed were ineligible.

Thirty-five patients were excluded from further analysis as they failed to complete all three treatment modalities. Their details are shown in Table 1.

Until 1986 the Price-Hill chemotherapy regimen...
Table 1. Patients who failed to complete triple therapy
(n = 35)

<table>
<thead>
<tr>
<th>Reason for cancellation</th>
<th>No. patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Delayed healing from surgery</td>
<td>7</td>
</tr>
<tr>
<td>Developed distant metastasis</td>
<td>4</td>
</tr>
<tr>
<td>Operative death</td>
<td>2</td>
</tr>
<tr>
<td>Refused</td>
<td>1</td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>2</td>
</tr>
<tr>
<td>Surgery</td>
<td></td>
</tr>
<tr>
<td>Clinical complete response</td>
<td>4</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Surgery and radiotherapy</td>
<td></td>
</tr>
<tr>
<td>Second malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Rapid progression of disease</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>2</td>
</tr>
<tr>
<td>Refusal by patient</td>
<td>3</td>
</tr>
<tr>
<td>Unknown</td>
<td>1</td>
</tr>
<tr>
<td>Refusal by patient of all treatment</td>
<td>4</td>
</tr>
</tbody>
</table>

was used but was subsequently replaced by cisplatin and 5FU because of an anticipated improvement in the response rate. The regimen was: cisplatin — 25 mg/m² on days 1–4 followed by 5FU — 1000 mg/m²/day given on days 1–4 and repeated again on days 28–32.

Response to chemotherapy was assessed according to WHO criteria. Complete response (CR) was defined as an absence of any clinically detectable disease; partial response (PR) represented a decrease in overall tumour dimensions of at least 50%. No change (NC) described a less than 50% reduction in size and progressive disease (PD) indicated a 25% or more increase in the size of one or more measurable lesions. Symptomatic improvement was also recorded and usually correlated well with gross appearance of the tumour.

Tumour bulk was measured at both the primary and metastatic site, the worse result being recorded. The assessment of response to treatment was sometimes difficult because the position of the tumour made accurate examination impossible.

The surgical resection was planned following histological classification and UICC staging. Most tumours were tattooed prior to chemotherapy to prevent possible compromise of the resection margins at surgery. The surgery was performed by two teams of surgeons; Otalaryngologists/Head and Neck surgeons who carried out the resection, and Plastic and General surgeons who performed the reconstruction using free flaps in the majority of cases (Table 2). In this way possible compromise in either the extent of excision or method of repair was avoided.

Radical external beam radiotherapy was given at the Queensland Radium Institute, Brisbane. Most patients began therapy within 6 weeks from the date of surgery. All cases received megavoltage external beam radiotherapy to the primary site and first echelon lymph nodes usually sparing the stomal area. The dose to the primary site varied: 50.5% of individuals received more than 60 Gy, 46% received between 50 and 59 Gy and 3.5% had less than 50 Gy. The lower cervical nodes were usually given 50 Gy and the daily fraction dose was between 2.0 and 2.2 Gy.

The minimum follow-up period was 2 years. Five year actuarial survivals were calculated using the Kaplan-Meier method with a Cox regression analysis used for the evaluation of possible prognostic factors.

Results

Details were available on 120 patients who were studied retrospectively although 35 patients were excluded as they missed one or more arms of the treatment (Table 1). The data from the remaining 85 cases are presented with pretreatment details shown in Table 3.

Table 2. Surgical repair

<table>
<thead>
<tr>
<th>Reconstruction</th>
<th>No. patients</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jejunum</td>
<td>49</td>
<td>57.6</td>
</tr>
<tr>
<td>Radial artery forearm flap</td>
<td>16</td>
<td>18.8</td>
</tr>
<tr>
<td>Myocutaneous flap</td>
<td>8</td>
<td>9.4</td>
</tr>
<tr>
<td>Primary closure</td>
<td>8</td>
<td>9.4</td>
</tr>
<tr>
<td>Split skin</td>
<td>2</td>
<td>2.4</td>
</tr>
<tr>
<td>Other</td>
<td>2</td>
<td>2.4</td>
</tr>
</tbody>
</table>

Table 3. Pre-treatment data of triple therapy patients
(n = 85)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Subdivision</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>Male</td>
<td>75</td>
</tr>
<tr>
<td></td>
<td>Female</td>
<td>10</td>
</tr>
<tr>
<td>Age (years)</td>
<td>Median</td>
<td>59</td>
</tr>
<tr>
<td>Site of primary</td>
<td>Oropharynx</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>Hypopharynx</td>
<td>26</td>
</tr>
<tr>
<td></td>
<td>Larynx</td>
<td>11</td>
</tr>
<tr>
<td></td>
<td>Oral cavity</td>
<td>6</td>
</tr>
<tr>
<td></td>
<td>Maxilla</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Combination</td>
<td>3</td>
</tr>
<tr>
<td>T stage</td>
<td>T1</td>
<td>3</td>
</tr>
<tr>
<td></td>
<td>T2</td>
<td>9</td>
</tr>
<tr>
<td></td>
<td>T3</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>T4</td>
<td>31</td>
</tr>
<tr>
<td>Nodal stage</td>
<td>N0</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>N1</td>
<td>33</td>
</tr>
<tr>
<td></td>
<td>N2</td>
<td>18</td>
</tr>
<tr>
<td></td>
<td>N3</td>
<td>2</td>
</tr>
<tr>
<td></td>
<td>Stage III</td>
<td>38</td>
</tr>
<tr>
<td></td>
<td>Stage IV</td>
<td>47</td>
</tr>
</tbody>
</table>
The 5 year survival for the 116 patients who started the triple therapy was 54%. The 5 year overall actuarial and relapse free survival of those completing all three modalities of treatment was 60% and 53% respectively (Kaplan-Meier; Figs 1, 2). There was no significant difference in survival by site although the numbers in each case were small.

**Fig. 1.** Actuarial 5 year survival for patients completing triple therapy.

**Fig. 2.** Actuarial 5 year relapse-free survival for patients completing triple therapy.

**CHEMOTHERAPY**

Fifty patients were given the Price-Hill regimen while 32 received cisplatin and 5 FU. Three patients had the chemotherapy in other units with no record of their treatment available. Eighty-two patients received two or more courses with an overall response rate of 24% for the Price-Hill regimen and 56.2% for the cisplatin/5FU. Of cases receiving
the Price-Hill regimen 3.6% responded completely compared with 23% for cisplatin/5FU. A histologically proven complete response was achieved in 8.2% of cases. Records of symptomatic response are incomplete although at least 35% of patients gained a significant improvement following the chemotherapy treatment.

The 5 year survival for the different chemotherapy regimens are shown in Fig. 3. The improvement with cisplatin and 5FU is statistically significant ($P < 0.05$) suggesting a positive therapeutic effect may have been achieved with this regimen rather than just a symptomatic improvement. The two chemotherapy regimens were used to treat an even distribution of primary tumour sites. The response to chemotherapy showed no correlation with either the site or stage of the primary tumour.

Two patients died following the Price-Hill regimen, one from renal and the other from respiratory failure. There were no cases of neutropenic sepsis or cardiac failure.

**SURGERY**

The operations comprised 40 pharyngolaryngectomies, five laryngectomies, 27 oropharyngeal resections and seven others which included resections of the maxilla and sinuses. Sixty-two radical neck dissections were performed for metastatic cervical lymph node involvement. Patients with bilateral neck disease had an ipsilateral radical neck dissection on the contralateral side.\(^7\)

Reoperation because of microvascular complications was unusual, occurring in only five cases. Two postoperative deaths occurred; the first due to septicemia in a patient who had previously had a splenectomy and the second due to a myocardial infarct 10 days postoperatively.

**HISTOLOGY**

Histological examination of the primary tumour specimens showed the excision margins to be clear in 65.9% and close ($<1$ mm) in 15.3% of cases. No patient had macroscopic evidence of residual tumour although microscopic deposits were present in 12.9% of cases. These were divided equally between the hypopharynx and oropharynx where occasionally the size of the tumour made total excision difficult if not impossible without significant associated morbidity. Unfortunately, details on excision margins were unavailable in a further 5.9% of cases. Vascular invasion was present in six cases, but this did not appear to adversely affect either survival or distant relapse.

Metastatic cervical lymph node involvement occurred in 67.6% of patients who had a neck dissection. Of these 93% had less than 5 nodes involved although the number showed no significant correlation with overall survival. The absence of nodal invasion by tumour may have been genuine or pos-

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**Fig. 3.** Actuarial 5 year survival for patients receiving (A) Price-Hill or (B) Cisplatin/5FU chemotherapy ($\chi^2 = 4.45$; $P < 0.05$).
possibly due to tumour necrosis from previous chemotherapy. Extracapsular spread was present in 7.7% of patients but did not adversely affect 5 year survival.

**DISTANT METASTASES**

These occurred in 17 patients, primary tumours of the hypopharynx and oropharynx being responsible for eight and six cases respectively. The other primary sites included the oral cavity and larynx. There was no difference in incidence among Stage III or IV tumours although 14 patients had previous lymph node metastases. Surgical excision margins also showed no correlation. The incidence of distant metastases were similar in patients with incomplete and complete primary excisions.

**RADIOThERAPY**

Radiotherapy was usually given within 6 weeks of surgery. There were no severe radiation reactions and 98.8% of patients completed their treatment as planned. Although there was no significant difference in survival between groups receiving less than 60 Gy and those receiving 60 Gy or more, there appeared to be a trend towards an improved survival with higher doses (Fig 4).

**SITES OF FAILURE**

The most common primary cause of failure was that of distant metastasis which occurred in 21% of cases followed by primary and nodal recurrence in 9.4 and 7% of patients respectively. The majority of distant metastasis (55%) occurred despite control at both the primary and regional sites. Of patients who relapsed, 87.5% died of progressive disease.

**MULTIVARIATE ANALYSIS OF PROGNOSTIC FACTORS**

A Cox multivariate regression analysis was performed to determine any factors which may improve long-term survival (Table 4). The only parameter which achieved prognostic significance ($P < 0.05$) was the chemotherapy regimen using cisplatin and 5FU.

**Table 4. Regression analysis of possible prognostic factors**

<table>
<thead>
<tr>
<th>Factor</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>NS</td>
</tr>
<tr>
<td>Sex</td>
<td>NS</td>
</tr>
<tr>
<td>T stage</td>
<td>NS</td>
</tr>
<tr>
<td>Nodal stage</td>
<td>NS</td>
</tr>
<tr>
<td>Chemotherapy regimen (Price-Hill, cisplatin/5FU)</td>
<td>$&lt; 0.05$</td>
</tr>
<tr>
<td>Surgical excision margins</td>
<td>NS</td>
</tr>
<tr>
<td>(clear, close, residual tumour)</td>
<td>NS</td>
</tr>
<tr>
<td>Radiotherapy dose ($&lt; 60$ Gy, $&gt; 60$ Gy)</td>
<td>NS</td>
</tr>
</tbody>
</table>

NS = not significant.

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**Fig. 4.** Actuarial 5 year survival for patients receiving (A) 55–59 Gy or doses (B) $> 60$ Gy ($\chi^2 = 0.7518$; not significant).
Discussion

The optimum management of Stage I and II head and neck tumours by single modality treatment is now well recognized and established. This is in contrast to the treatment of advanced disease which remains controversial. Following definitive treatment, patients tend to relapse both locoregionally and at distant sites. Individual therapeutic modalities have shown few great advances over the past 20 years and clinicians therefore, looked to the use of combination treatment in the hope of improving long-term survival.

Chemotherapy

Chemotherapy has several theoretical advantages. In many cases it reduces the bulk of tumour thus increasing tumour oxygen saturation and subsequent sensitivity to radiotherapy; there is also the hope that it may sterilize micrometastasis which may have spread pre-operatively.

There have been many randomized controlled studies which have examined the use of induction chemotherapy in the treatment of head and neck cancer. The results from the individual studies although showing a trend towards improved survival have failed to show any significant difference when compared with controls. Stell has shown that this is probably due to the limited numbers in each study which are therefore not powerful enough to detect the expected small improvement. Using a meta-analysis technique whereby the results of different studies are pooled, Stell has shown that a 3% decrease in cancer mortality could be achieved but only with synchronous or synchronous/maintenance chemotherapy regimens. Therapy courses given as induction or as induction/maintenance appeared to have no effect on cancer mortality.

Other investigators have pointed out the short duration of response to chemotherapy shown by head and neck tumours; this suggests a limited cell kill presumably due to the presence of numerous drug resistant subpopulations. The number of surviving cells therefore, is likely to be considerable and not surprisingly no significant increase in survival has been shown.

Since this was an uncontrolled study the effects of induction chemotherapy on long-term survival in this series are unknown. The cisplatin/5FU regimen showed a positive correlation with prognosis although this could be due to the Price-Hill regimen having a negative effect on survival as suggested by the two deaths in this study and results from previous trials. With a change of treatment this effect would have been negated.

Previous reports have suggested that response to chemotherapy may be used as a prognostic indicator since complete responders appear to have a significantly better long-term survival. These studies were non-randomized however, and when correcting for differences in expected 3 year disease-free survival based on site and stage Taylor found the difference to be non-significant.

The results of this series show no significant correlation between response to chemotherapy and long-term survival although the seven patients who showed a histological complete response achieved a 100% 5 year survival.

One of the major concerns of chemotherapy is the possible increase in morbidity and mortality secondary to their associated toxicity. A review of previous trials using several different chemotherapy regimens shows an associated average mortality of 6.5% which must be offset against any improvement in survival which may be achieved. In this study there were two deaths from the Price-Hill regimen giving an overall mortality of 2.4%.

The majority of patients however, experienced few side effects and many (36%) achieved a reduction in size of the tumour with a consequent improvement in their symptoms and feeling of well-being. Although higher response rates have been achieved using three courses of chemotherapy these have shown no benefit in regard to long-term survival and have the added disadvantage of increasing an already lengthy treatment regimen. The chemotherapy had no effect on postoperative morbidity and tended to make the surgical resections easier because of a reduction in size of the tumour.

There was early optimism that chemotherapy would overcome distant micro-deposits of tumour inaccessible to other forms of treatment. In this way a reduction in the incidence of distant metastases, which occur in up to 30% of cases with Stage IV disease, could be achieved. This hope appears to have been ill-founded since distant metastasis occurred in 21% of patients within 5 years postoperatively. This finding agrees with other studies which have failed to show any significant decrease in the incidence of distant metastasis with the use of chemotherapy.

Surgery

A major advance in the surgical treatment of head and neck cancer occurred with the development of microvascular free flaps restorative techniques. This permitted not only more extensive resections but also improved the quality of repair. The team approach adopted by this unit has eliminated any compromise in either the resection or the repair of these advanced tumours. Free flaps have been used extensively in many reconstructions (Table 2) with a few complications (6%) and a more functional end result.
A significant number of patients with advanced head and neck tumours have associated bilateral nodal disease. These patients were treated by radical neck dissection on the ipsilateral side with a functional neck dissection on the contralateral side. In the latter case the internal jugular vein, sternomastoid muscle and accessory nerve were preserved. These patients showed a regional recurrence rate of 12% after an average follow-up of 49.6 months. This compares well with the 11% regional failure rate after radical neck dissection found in this series.

RADIOThERAPY

Radiotherapy was given postoperatively, the dose to the primary site falling into two major groups: those who received more than 60 Gy and those who received less than 60 Gy. Interestingly the former group appeared to show a trend toward a better survival with no increase in the severity of side effects.

The variation in radiotherapy dose was due to individual patient criteria rather than a failure to complete treatment. Fifty gray is sufficient to sterilize microscopic disease in the unoperated neck although a higher dose is required postoperatively presumably due to the increased number of hypoxic cells in scar tissue.

The treatment was usually started within 6 weeks of completion of surgery. Vikram has shown that a delay in the start of radiotherapy postoperatively beyond 6 weeks decreased the level of local control with a consequent increase in mortality. Although some cases fell outside this time period the numbers were small and this had no effect on long-term survival.

SITES OF RELEASE

Distant spread was the major cause of relapse in these patients mostly occurring despite locoregional control. The occurrence of distant metastasis appeared to be related to, not only tumour bulk at the primary site, but also the tendency to spread. The majority of these patients had extensive nodal metastasis at initial presentation suggesting that they represent a particularly aggressive subset of tumours. This has been reported by other investigators who consider that nodal involvement could almost be considered a prognostic indicator of metastatic spread.

Conclusions

This paper presents the experience of this Unit using triple therapy in the management of advanced head and neck cancer. The 60% 5 year survival results support the continued use of combined therapy and compare well with the 44% 3 year survival achieved by other investigators using hyperfractionation radiotherapy alone.

Randomized trials have not shown an improved survival with adjuvant chemotherapy. However, chemotherapy leads to an improvement in the patient's pre-operative condition without progression of the disease. There is often a symptomatic improvement with a subsequent nutritional gain coupled with a cessation of alcohol and cigarette consumption.

Current therapeutic modalities appear to achieve a good locoregional control with distant spread now having the main effect on survival. Tumours vary in their aggressiveness suggesting that factors associated with the tumour, or host, or a combination of the two, play a significant role in contributing to their tendency to spread.

Recent research has emphasized the importance of DNA content in determining long-term survival and future work should be directed more towards the study of intrinsic tumour biology and aspects of host response since this is likely to be the next era of therapeutic breakthrough.

Acknowledgement

The help of Mr Lee Tripony is gratefully acknowledged in the statistical analysis for this study. The authors would also like to thank the other members of the team who were involved in managing these patients: Dr T. Cooney, Dr G. McCafferty, Dr D. Szallasi, Dr D. Thiele, Dr M. Hughes, Dr D. Thomas, Dr G. Dickie, Dr G. Beadle, Dr P. Barnes and Dr G. McDermant.

References


