The role of chemotherapy in squamous cell carcinomata of the head and neck has been undergoing intensive re-evaluation during the last decade. The traditional approach to treatment of head and neck cancer involved some form of surgery, preceded or followed by radiotherapy. In the one-third of patients presenting with local disease, the use of such measures resulted in a significant cure rate. However, most patients present with advanced stage III or IV local and regional disease. Although combined surgery and radiotherapy have provided greater local control, the incidence of local failure remains high, at 70%, and distant metastases develop in 20-30% of patients (Probert, Thompson and Bagshaw, 1974; Grunberg, 1985). Therefore, in spite of the best local therapy, most patients with squamous cell carcinoma of the head and neck die from their disease.

Traditionally, only patients with recurrent or disseminated head and neck tumours were considered eligible for chemotherapy. These patients have a poor prognosis, with an average survival period of six months or less. Despite the fact that several antitumour drugs have proved highly effective in shrinking bulky lesions, palliative chemotherapy, using single agents, has had no impact on the survival rate. Indeed, not for several decades has this traditional approach to the management of head and neck tumours resulted in any overall improvement in disease-free survival rates. Identification of a large number of active single agents and their potential in drug combinations has led to consideration of a new role for chemotherapy. This chapter reviews these developments and describes a logical scientific approach towards earlier integration of safe and optimum chemotherapy into a multidisciplinary attack, in an attempt to improve the prognosis for this group of tumours.

Traditional approach to chemotherapy in advanced disease

The evaluation of chemotherapy data pertaining to head and neck cancer is complicated by the heterogeneity of prognostic variables associated with this tumour type (Carter and Livingstone, 1982). These include: the site of the primary lesion, the clinical stage, prior therapy, and nutritional and performance status. Most studies report on a relatively small number of patients so that the analysis of response, even according to only one of these parameters, leads to numbers which are too small to be meaningful. The overall impression is that each of these variables may be prognostically significant.

Single agents

The history of chemotherapy for head and neck cancer began with a demonstration that methotrexate was capable of shrinking clinically evident tumour masses. Results from many studies have established an approximate 40% response rate to this agent, although the optimal schedule is still not known. The general recommendation for routine administration with acceptable toxicity is for methotrexate to be used systemically, in moderate dose, on an intermittent basis. This avoids the definite morbidity associated with intra-arterial cannulation. Bertino, Boston and Capizzi (1975), in a detailed analysis by site, reported the highest response rates to methotrexate in oral cavity and oropharyngeal lesions, and the lowest in nasopharyngeal and hypopharyngeal tumours. The response duration was longest (four
months) in tonsillar and oral tongue lesions, and was shortest (two months) in tumours of the palate, oropharynx, floor of mouth and hypopharynx.

Bleomycin is the second most studied single agent in head and neck cancer. In 298 accessible patients, 48 showed a 25% response or greater, 54 showed responses of 50% or greater and 10 had a complete response (Carter, 1977). The highest rates were noted in tumours of the tonsil, nasopharynx and sinuses, while the longest durations of response (four to six months) were seen in tonsillar, palatal and nasopharyngeal lesions. The optimum dose of bleomycin in this compiled study was considered to be 0.25-0.50 units/kg administered weekly or twice weekly by either intravenous or intramuscular routes.

Cisplatin is the newest single agent to demonstrate definite activity in head and neck cancer (Carter and Livingstone, 1982; Million, Cassissi and Wittes, 1985). Its major toxicities are nausea and vomiting, dose-related renal damage and ototoxicity. These side-effects can be reduced by appropriate antiemetics, prehydration and diuresis. Cisplatin is effective when administered intravenously over 30-60 minutes or as a 24-hour infusion. A recent randomized study (Veronesi et al, 1985), confirming earlier reports, found no evidence of drug-dose dependency, which would suggest that patients may be spared the toxicity of high dose cisplatin without a consequential undermining of their chances of benefiting from treatment.

Data on the remaining standard antitumour drugs are far less extensive with some activity indicated with cyclophosphamide, doxorubicin (Adriamycin), vinblastine, dibromodulcitol (Mitolactol) and the newer agent methylglyoxal bisguanylhydrazone (methyl-GAG). For most drugs tested, only small numbers of patients were evaluated and response rates of less than 20% reported.

It must be emphasized that nearly all these studies were carried out on patients with recurrent and previously treated disease. Although respectable response rates have been achieved in a significant number of patients treated with methotrexate, bleomycin or cisplatin, the median durations of response have been of the order of three to six months only. In the few reported randomized studies comparing these three agents, no major differences in response or survival rate have been noted, although methotrexate was much better tolerated than cisplatin, and the lack of myelosuppression associated with bleomycin was considered particularly beneficial. In an attempt to improve the results, combinations of drugs were tested next in advanced disease.

**Drug combinations**

Many different drug combinations have been tried in advanced head and cancer, based mainly on the following agents: methotrexate, 5-fluorouracil, cisplatin, bleomycin and vincristine. Reported response rate range from 14% to 73%, thereby providing an indication of increased overall response rates with combination chemotherapy as opposed to single agents. However, durations of response remain short, that is about six months. Furthermore, in the few reported randomized studies comparing single agents with combinations of drugs, no significant differences were reported in response or survival rates, and in certain cases the drug combinations were associated with increased toxicities.
The conclusion to be drawn from these studies, using the traditional approach in managing advanced tumours of the head and neck, is that, in spite of an occasional dramatic response rate being achieved with specific antitumour drugs, there has been considerable morbidity and no significant increase in the survival rate. The next step forward has involved a more logical approach to the use of chemotherapy, based on certain principles derived from experimental and theoretical studies.

**A logical scientific approach to optimal adjuvant combination chemotherapy**

Although the search for new agents or combinations of agents continues, it is the more logical use of drugs already available which offers the best prospect for increasing survival times, and even cure rates. This approach is based on certain recent advances in tumour biology, results from experimental animal studies and theoretical concepts of drug resistance.

**Experimental studies with clinical relevance**

**Rationale for the combined modality approach**

In many experimental animal tumours and certain human tumours, where accurate measurements have been possible, there is a constant relationship between the increase in tumour cell number and time period, and these cells are said to grow exponentially. Exponential growth is especially characteristic of the early period of tumour development, but as the tumour mass increases, the growth rate tends to slow. The figure provides a diagrammatic representation of the correlation between tumour cell number and tumour weight, the ability to detect the tumour clinically and the death of the patient. Present methods of investigation in man are unable to detect tumours until about 1 g of tumour is present, consisting of approximately $10^9$ cells. As the patient is likely to die when the total tumour burden reaches between $10^{12}$ and $10^{13}$ cells (that is 1-10 kg tumour weight), it follows that, by the time the tumour can be detected, it is already at least two-thirds of the way through its lifespan. By definition, most tumours are late or advanced at the time of presentation. The same theoretical point applies to the detection of secondary deposits of all tumour cells not removed or destroyed by local therapy. This, therefore, provides an explanation of why even the best techniques of surgery and/or radiotherapy have been unable to cure many advanced head and neck cancers, as undetectable malignant cells will have been left behind. It follows, therefore, that any attempt to increase the cure rate must include a systemic form of treatment, namely antitumour drugs, as part of the initial combined attack on the tumour.

**Rationale for optimal adjuvant chemotherapy**

Experimental animal studies as early as the mid-1950s provided evidence in favour of combining local therapy with chemotherapy (Shapiro and Fugmann, 1957). Subsequent studies in the 1960s by Skipper, Schabel and Wilcox (1965) emphasized that this combined approach was more effective against smaller tumours than against larger ones, and that superior results were produced with 'full-doses' of drugs. To summarize, these studies showed that chemotherapy was optimal when full-dose intensive drug combinations were used to treat unrecognized regional or metastatic disease before the latter became clinically evident. This use of chemotherapy has been termed 'adjuvant chemotherapy' and, in this chapter, the term is used to describe the administration of antitumour drugs before, during or immediately after...
local treatment by surgery and/or radiotherapy. These experimental studies also showed that suboptimal adjuvant chemotherapy, like any other kind of inadequate treatment, produced inadequate results.

More recently, Goldie, Coldman and Bruchovsky (1983) have described a mathematical model relating the probability of curing a tumour with drugs to the length of time that the tumour has been present. Essentially, the model proposes that as tumour cells multiply there is an increased likelihood of cells with drug-resistant phenotypes emerging by chance. The probability of cure is high early in the lifetime of the tumour, but as the tumour increases in size the number of drug-resistant mutants also increases and, consequently, the probability of cure falls sharply, ultimately reaching zero. Combination chemotherapy will have the effect of reducing the mutation rate, thereby making treatment more effective. In summary, this work emphasizes that any delay in starting chemotherapy will greatly reduce the likelihood of 'cure'. Adjuvant combination chemotherapy should be started in conjunction with, or should even precede, the local attack on the primary tumour. Furthermore, Goldie and coworkers (Goldie, Coldman and Gudauskas, 1982; Goldie, Coldman and Bruchovsky, 1983) have shown, in an extension of their model, that prolonged therapy with a single agent (or combination of agents), which allows the unimpeded growth of subpopulations resistant to it, will increase the probability of mutants developing which are resistant to all available therapies. Therefore, when a number of drugs are available which cannot be used simultaneously - perhaps, for example, because of toxic side-effects - then the most effective strategy for delaying or preventing the emergence of drug-resistant tumour cells is to administer two equally effective combinations alternately and not sequentially. This has led to the testing of 'alternating non-cross-resistant drug combinations'.

These observations have major implications for future adjuvant studies, showing how chemotherapy can be used more logically and more acceptably. Verification of these predictions rests on appropriate clinical studies.

Rationale for administering safe, yet effective, combination chemotherapy

One of the main objections to adjuvant chemotherapy has been that the use of antitumour drugs is associated with extremely toxic side-effects. However, there now exists a proven method of giving intensive chemotherapy much more safely than in the past (reviewed in Price, hill and Ghilchik, 1981; Price and hill, 1983, 1985). This major contribution to chemotherapy, in terms of safety and minimal toxicity to normal bone marrow stem cells, has come from the clinical application of certain fundamental experimental concepts of cell cycle kinetics. Stem cells, by definition, have the capacity for unlimited proliferation. It is the stem cell population which is responsible for maintaining the integrity and continued survival of any population (reviewed in Hill, 1978). The object of chemotherapy is to inflict the maximum damage to malignant stem cells while doing minimal damage to normal stem cells. In the 1960s, a technique was developed which enabled a comparison to be made between the differing effects on the survival of the normal bone marrow stem cells and lymphoma stem cells in tumour-bearing mice, of a 24-hour exposure to various chemotherapeutic agents (Bruce, Meeker and Valeriote, 1966). Results showed that drugs could be divided into two categories: those which, after an initial reduction in survival rate, did not cause increasing damage to normal bone marrow stem cells with increasing dosage (class II); and those where the bone marrow stem cell kill was accelerated with
increasing dosage (class III). In both cases, there was maximal selective kill of malignant stem cells. This selectivity appeared to be based on the fact that, in untreated mice, most of the normal haematopoietic stem cells were resting, while all the detectable lymphoma stem cells appeared to be cycling. Therefore, short courses (that is over 24 hours) class II and class III drugs would cause a much greater kill of malignant as opposed to normal stem cells. If the time of drug exposure is prolonged, however, this kinetic difference between normal and malignant stem cells is abolished and increasing damage to the normal bone marrow occurs. These initial studies have now been extended to include other agents (reviewed by Hill, 1978) and form the basis for a kinetic classification of antitumour drugs. The table classifies the drugs used in the treatment of head and neck cancer. Bleomycin and hexamethylmelamine have not been included as data suggest that they have little effect on normal bone marrow stem cells.

The experimental findings from this model system show that the following principles should be applied in the chemotherapy of head and neck cancer.

1. Chemotherapy should be given over periods of 24-36 hours in intermittent courses (at approximately 2-3 week intervals) as this approach would markedly reduce toxicity and lead to safer chemotherapy.

2. A knowledge of the kinetic classification of antitumour agents is essential if chemotherapy is to be safely administered. The toxicity of class II agents to normal stem cells (for example bone marrow) is not dose dependent. Class II drugs may, therefore, be added to combinations without necessitating a reduction in their dose, provided that the total treatment does not exceed 24-36 hours. Combinations of class III drugs will be additively toxic to normal bone marrow and doses should, therefore, be reduced proportionately.

3. The practice of giving small daily doses of drugs from either class should be avoided, as under these conditions normal bone marrow stem cells will be drawn into the cycle and killed. This approach would increase the toxicity to normal bone marrow and may reduce the number of malignant cells that are killed because the treatment has to be postponed or interrupted.

Clinical implications of these theoretical concepts

The theoretical points outlined previously show that chemotherapy can be given much more safely than in the past and also that it should be given early in the disease, that is either before, in conjunction with, or as soon as possible after, local treatment. The traditional use of drug therapy in head and neck cancer should be reviewed and replaced by the logical approach shown in the figure. In this way, the safe integration of chemotherapy into a combined attack with surgery and radiotherapy can be achieved in head and neck cancer.
Figure. A suggested approach towards the integration of chemotherapy with surgery and/or radiotherapy in a multidisciplinary attack on head and neck cancers

- Identify potentially effective drugs from available clinical and/or experimental data.
- Optimize chemotherapy protocol for maximum safety and efficacy.
- Integrate optimal chemotherapy protocol with surgery and/or radiotherapy. Use as a primary treatment of 'bad-risk' local and regional disease. Evaluate in large, randomized, prospective controlled clinical trials.

**Clinical results using this scientific approach**

The aforementioned principles have direct clinical application, whether head and neck cancer is treated with single agents or with drug combinations. For example, it is possible to give methotrexate in very high doses with increased therapeutic effect provided that certain precautions are rigorously observed. A safe approach is to infuse the drug in 1-2 litres of normal saline over periods of 12-30 hours in doses of 100-20,000 mg, followed by folinic acid 'rescue' (Goldie, Price and Harrap, 1972). It is essential to maintain a good diuresis during the infusion and to extend the folinic acid rescue appropriately in patients with impaired renal function, as judged by low creatinine clearance (Price and Hill, 1977). Similarly, up to 40 g of hydroxyurea, a class II agent, can be given over 24 hours (Hill and Price, 1982).

The greatest step forward, however, in terms of the response rate, has been the use of the foregoing concepts in designing combination chemotherapy protocols which are not only safer but also more effective than previous multiple drug treatments given over several days. In 1975, the use of a seven-drug kinetically designed combination produced not only an 80% response rate in advanced squamous cell carcinoma (T3 and T4 lesions in the TNM classification), but also caused no significant myelosuppression (Price et al, 1975). Forty per cent of the patients in this study survived for at least one year, even though they were all considered 'terminal' when treatment was started.

Therefore, contrary to widespread belief, even among 'experts', intensive chemotherapy can be given with safety, provided that the standard medical precautions, listed in the table are rigorously observed. Furthermore, the authors' 24-hour approach has enormous advantages for the patient, and these are as follows: patients spend only one night in hospital every three or four weeks; there is no serious myelosuppression, thus obviating the need for intensive supportive therapies, such as platelet transfusions and antisepticaemia regimens; the patients spend 90% of their time at home and can plan their lives accordingly; and there is no loss of therapeutic effect. Several other groups (Bezwoda, de Moor and Derman, 1979; Shah et al, 1979; Malaker, Robson and Schipper, 1980; Sergeant and Deutsch, 1981) have now confirmed the efficacy and significant lack of toxicity using either the present authors' original seven-drug protocol or a modified version (schedule A chemotherapy).
Table. Precautions to be observed in all cases receiving chemotherapy

(1) Never give another treatment unless the peripheral blood count has returned to its original level.

(2) Patients with impaired renal function receiving methotrexate must have an extended folinic acid 'rescue', that is at least 3 hours longer than normal.

(3) Doses of cyclophosphamide, doxorubicin (Adriamycin) and 5-fluorouracil should be halved in patients who have had thoracic, abdominal or pelvic irradiation.

(4) Doses of class III agents should be reduced proportionately if more than one of them is included in a combination.

(5) Doxorubicin should not be given to patients with a history of cardiac failure. The total dose of doxorubicin must never exceed 550 mg/m². The dose of doxorubicin should be halved in patients who have impaired hepatic function.

(6) Patients receiving drugs which are excreted in the urine, for example methotrexate, cisplatin and hydroxyurea, must be adequately hydrated and passing urine while they are having the drug.

(7) Bleomycin should not be given to any patients with impaired respiratory function.

It is of major significance, however, that this 24-hour method of administering antitumour drugs has definite implications for optimal adjuvant chemotherapy, as summarized in the table.

Table. Advantages of the 24-hour approach to adjuvant chemotherapy

(1) Full-dose intensive combination chemotherapy can be administered early and safely.

(2) Intervals between the courses of chemotherapy can be the minimum consistent with clinical tolerance for the first few cycles, since there is no severe myelosuppression.

(3) These chemotherapy protocols can be integrated successfully and safely with surgery or radiotherapy.

(4) The 24-hour approach can be used in designing alternating non-cross-resistant combination chemotherapy protocols.

Indeed, the present authors have now carried out a detailed evaluation of a simplification of the 1975 protocol, using a kinetically sequenced combination of vincristine, bleomycin, methotrexate, 5-fluorouracil and hydrocortisone (schedule A) given over 24 hours with a folinic acid 'rescue' as initial treatment in advanced head and neck cancer (Price and Hill, 1977, 1982; Hill, Price and MacRae, 1986). Two hundred and eight patients have now been entered into this study. Chemotherapy was administered on days 1 and 14 before
'curative' local therapy. Toxicity was minimal and patient compliance was 100%. Chemotherapy response was assessed in 200 patients on day 28: 132 (66%) had an objective response and 68 (34%) were judged as non-responders. The complete remission rate following local therapy was significantly greater in chemotherapy responders (49%), \( P < 0.001 \). The overall seven-year survival time of this entire patient group was 33%, with median survival figures of 32 months for all patients, 37 months for all chemotherapy responders, and 69 months for all patients achieving a final complete remission. Analysis by tumour site shows that patients with oral cavity or nasopharyngeal tumours responded well to initial chemotherapy (\( P < 0.05 \) and \( P < 0.01 \)) compared with those with tumours at all other sites. This high response rate was not, however, necessarily associated with increased survival, for although the median survival time in patients with nasopharyngeal tumours was 64 months, in the case of oral cavity lesions, the median survival time of chemotherapy responders was only 22 months. Furthermore, the longest median survival time was observed in patients with laryngeal tumours, in spite of these patients having had one of the lower response rates to initial chemotherapy. Therefore, in this series, survival figures are markedly influenced by the tumour site, and the response to initial chemotherapy is not automatically a favourable prognostic sign.

The authors' result would appear to indicate that initial schedule A chemotherapy may be of significant benefit in prolonging good quality life for patients with tumours at certain specific sites, for example in the larynx and nasopharynx, but not at others. Different chemotherapy protocols may be required for tumours at other sites. On the basis of these data, it is suggested that squamous cell carcinomata of the head and neck should no longer be grouped as if they were a single disease entity, but that randomized, prospective, controlled clinical trials should be carried out using initial chemotherapy protocols to see which particular sites would benefit in terms of increased good quality survival.

**Combined modality approaches**

Head and neck cancer is a disease in which many various combinations of drugs with surgery and/or radiation outlined in the figure have been considered. The increasing evidence that chemotherapy given after surgery and radiotherapy is poorly tolerated, and is associated particularly with severe local toxicity, has meant that the two most favoured approaches have involved the use of initial induction chemotherapy before local treatment, or the synchronous use of chemotherapy and definitive irradiation, with salvage surgery as appropriate. The alternative strategy, that of using chemotherapy after complete response has been achieved by means of primary local therapy, has not been widely tested, mainly because of associated side-effects. Indeed, Ervin, Clark and Weichselbaum (1985) reported that 50% of patients refused 'adjuvant' chemotherapy under these circumstances on account of the toxicity and disability induced by surgery and/or irradiation. It is significant also that in a large randomized trial, with one arm consisting of one initial course of cisplatin plus bleomycin, followed by eight cycles of cisplatin after local control, exceedingly poor compliance was reported (Jacobs et al, 1984).
Figure. Multidisciplinary approach to advanced squamous cell carcinoma of the head and neck.

- Induction chemotherapy to maximum response --> Local treatment --> Follow-up
- Fixed number of courses of induction chemotherapy --> Local treatment --> Adjuvant chemotherapy for complete responders
- Synchronous chemotherapy and irradiation --> Salvage surgery as indicated.

**Initial induction chemotherapy**

There are a number of theoretical advantages to using induction chemotherapy, some of which have already been discussed, and they are summarized in the table.

**Table. Theoretical advantages of using induction chemotherapy**

1. The intact vascular supply to the tumour present before radiation or surgery might allow better vascular access of the drugs to the tumour.

2. The generally better nutritional status and performance status of patients earlier in the course of their disease might permit effective chemotherapy to be given.

3. Chemotherapy response of the previously untreated tumour can be determined and this might serve as a chemosensitive assay *in vivo* which could direct later therapy.

4. Treatment of the tumour with chemotherapy early in the course of the disease might allow eradication of micrometastases prior to the development of drug-resistant clones.

5. Reduction in size of the tumour might allow surgery or radiotherapy that would not previously have been possible.

6. Preoperative shrinkage of the tumour might help the surgeon and/or radiotherapist to reduce the extent of locoregional therapy, thereby decreasing local morbidity and mutilation.

Initial induction chemotherapy has now been widely tested in previously untreated patients with locally advanced stage III and IV head and neck tumours, with reported response rates ranging from 60% to 90%. These results are clearly superior to those achieved in patients who have undergone prior surgery and/or radiotherapy. Several studies have confirmed that, after such induction chemotherapy, it is feasible to proceed to either surgery or radiotherapy, or to both, without any obvious increase in morbidity. The higher complete remission rate noted among responders to chemotherapy in many of these studies argues in favour of this approach, resulting in increased local control with subsequent surgery or radiotherapy. However, at present, induction chemotherapy should still be considered as additional treatment to *standard* surgery and radiation. Local treatments should not be changed because of tumour reduction following induction chemotherapy. Furthermore, firm evidence that these high initial response rates translate eventually into increased overall
survival rates is still not available. It is unfortunate that the great majority of reported induction chemotherapy trials are, in fact, only pilot studies with a small number of patients and a relatively short follow-up. The authors' results obtained by using schedule A chemotherapy in the largest reported series with the longest follow-up, compare very favourably with data from other studies. However, these pilot studies, while providing interesting leads, do not justify the use of initial drug treatment as part of everyday practice but rather point to the requirement for large-scale randomized trials.

The necessity for large numbers of patients to be incorporated into such studies is frequently stated and can also be appreciated by considering the many variables which need to be evaluated (see the table). Unfortunately, there have been relatively few reports of the successful setting up of multicentre studies.

**Table. Variables in induction chemotherapy trials.**

<table>
<thead>
<tr>
<th>Tumour characteristics</th>
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<tbody>
<tr>
<td>Site</td>
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<td>Stage</td>
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<tr>
<td>Differentiation</td>
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<table>
<thead>
<tr>
<th>Patient characteristics</th>
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<tr>
<td>Age</td>
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<td>Sex</td>
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<tr>
<td>Nutritional status</td>
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<tr>
<td>Performance</td>
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<table>
<thead>
<tr>
<th>Drug treatment</th>
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</thead>
<tbody>
<tr>
<td>Drugs selected</td>
</tr>
<tr>
<td>Number of induction cycles</td>
</tr>
<tr>
<td>Route of administration</td>
</tr>
<tr>
<td>Dose intensity</td>
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<table>
<thead>
<tr>
<th>Local treatment</th>
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<tbody>
<tr>
<td>Surgery only</td>
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<tr>
<td>Radiotherapy only</td>
</tr>
<tr>
<td>Surgery --&gt; radiotherapy</td>
</tr>
<tr>
<td>Radiotherapy --&gt; surgery</td>
</tr>
<tr>
<td>Criteria for operability</td>
</tr>
<tr>
<td>Surgical technique</td>
</tr>
<tr>
<td>Radiation dose and schedule</td>
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<table>
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<tr>
<th>Chemotherapy after local treatment(s)</th>
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<tbody>
<tr>
<td>Included or excluded</td>
</tr>
<tr>
<td>Drug(s) selected</td>
</tr>
<tr>
<td>Pre- or postradiotherapy.</td>
</tr>
</tbody>
</table>

The most commonly used preoperative chemotherapy protocols have included cisplatin. Response rates as high as 80-90% have been reported, in spite of the fact that most of these studies have involved fewer than 100 patients. Considerable interest has recently been created by the very high complete response rate (approximately 54%) achieved with three courses of initial chemotherapy consisting of cisplatin plus a 5-fluorouracil infusion (Kish et al, 1984). Median survival had not been achieved in this group of patients at 18 months, but the results
of long-term follow-up are awaited. It remains to be established whether higher complete response rates achieved by chemotherapy alone produce improved survival figures. The authors' observation that a high response to initial schedule A chemotherapy does not necessarily translate into an increased survival rate, for example in oral cavity lesions, emphasizes the heterogeneity of this group of tumours (Hill, Price and MacRae, 1986). The value of chemotherapy programmes in head and neck cancer should, therefore, be based on significant prolongation of good quality life and not just on achievement of high initial response rate.

Monitoring of good quality survival raises the question of toxicities associated with the administration of initial induction chemotherapy. Many authors consider that the toxicity associated with their protocols is acceptable. However, a survey of some recent presentations shows that significant toxicity is frequently associated with cisplatin-containing protocols. Therefore, in evaluating initial chemotherapy programmes, there is a need to justify, in randomized studies, the now almost automatic inclusions of cisplatin, by demonstrating improved survival figures.

Objective evidence of the effects of this combined modality approach on overall survival awaits definitive results from large, randomized, prospective, controlled clinical studies. Although preliminary results from a few of these randomized studies are not very encouraging, they do show that single-agent methotrexate or a single course of an initial cisplatin and bleomycin combination are inadequate (Jacobs et al., 1984; Taylor et al., 1985). Therefore, the impact of optimal initial chemotherapy in these tumours remains to be established.

**Synchronous chemotherapy and radiation therapy**

An extensive literature on the combination of irradiation with chemotherapy, dating back many years, is available. In the past, the most commonly used drugs were methotrexate, 5-fluorouracil and hydroxyurea and, in a review of these studies, Goldsmith and Carter (1975) reported somewhat contradictory, but essentially negative, results. These studies were designed to test the hypothesis that such antitumour drugs were acting as radiation sensitizers which would improve both the extent and duration of local control. However, patients demonstrated a poor tolerance of these therapies on account of moderate to severe local toxicities that frequently necessitated the interruption of planned radiation treatment. More recently, the concurrent use of drugs, such as bleomycin, 5-fluorouracil and cisplatin, with irradiation has received renewed attention. Evidence from studies *in vitro* has also indicated that these drugs can potentiate the killing effects of ionizing radiation. Recent studies of synchronous irradiation and chemotherapy are summarized in the table. By altering the irradiation schedules to include occasional breaks in treatment, and by using chemotherapy on as many radiation treatment days as possible, it would appear that the local toxicities (mucositis, skin reaction, radionecrosis) can be more readily controlled (Ervin, Clark and Weichselbaum, 1985). Therefore, encouraging data from some of these small pilot studies have provided the impetus for larger prospective studies. The Northern California Oncology Group is currently performing a prospective study comparing 7000 cGy alone to 7000 cGy plus bleomycin in patients with stage III and stage IV disease who are deemed to be inoperable (Carter, 1985). The code has not been broken, but one arm seems to be superior. In addition, the Eastern
Cooperative Oncology Group has begun a randomized trial of radiation alone against cisplatin with radiation (Taylor, 1984).

It would appear that chemotherapy combined synchronously with radiation, in schedules that allow for intermittent repair of sublethal injury to normal tissues, represents another avenue in the treatment of head and neck tumours which needs to be more thoroughly explored.

**Current trends and prospects**

The 1980s should be the decade in which head and neck cancer is added to the list of curable tumours. This is most likely to be achieved when there is full cooperation between surgeons, radiotherapists and medical oncologists.

There is ample evidence that head and neck tumours respond to currently available anti-tumour drugs and that the highest response rates are obtained using chemotherapy 'up-front'. The need remains to find effective salvage regimens for recurrent disease. However, the main focus of attention must be on obtaining improved good quality survival figures in previously untreated patients. As these studies must involve large numbers of patients, it is essential that multicentre trials are organized and encouraged. It could then be established whether:

1. it is necessary to include cisplatin, with its associated toxic side-effects, in initial combination chemotherapy or whether comparable results can be achieved using combinations of other drugs

2. certain chemotherapy protocols are particularly beneficial for tumours at specific sites within the head and neck region

3. increased complete response rates to initial chemotherapy improve survival

4. the use of initial chemotherapy and radiotherapy or synchronous drugs and radiation can replace surgical intervention and minimize mutilation for tumours at certain sites

5. the identification of a safe and effective chemotherapy protocol and its use after initial chemotherapy and the completion of local therapy will improve overall survival figures.

In this way, the initial benefits of chemotherapy in head and neck cancer can be fully realized and lead to the successful achievement of an increased cure rate in the near future.