and all patients subsequently received mediastinal radiation. Analysis after entry of 60 patients showed a major median survival benefit for patients treated with pre-operative chemotherapy (26 versus 8 months, $P<0.001$) such that the trial was stopped prematurely [10]. In the second trial, of similar design, patients treated with six cycles of pre-operative chemotherapy (cyclophosphamide, etoposide and cisplatin) had an estimated median survival of 64 months compared with 11 for patients treated with surgery alone ($P<0.008$) and again the trial was stopped early following entry of 60 patients [11]. These results require cautious interpretation, principally because of the very small number of patients. Nevertheless, two trials, albeit small, both reporting similar findings carry considerable statistical power, and further data in this important area are urgently required.

In terms of patient numbers, primary/neoadjuvant chemotherapy prior to radiotherapy may have a more important role than before surgery. In the last few years, two large randomised trials in patients with locally advanced NSCLC have reported significant survival improvement. In a CALGB trial, chemotherapy before radiotherapy was associated with a 43% improvement in median survival and a three year survival of 23% versus 11% [12]. Similarly, in a French trial, patients pretreated with three cycles of vindesine, cyclophosphamide, cisplatin and lomustine prior to radiotherapy had a modest but statistically significant survival improvement up to 3 years after treatment ($P = 0.08$) [13]. An MRC overview analysis of all such trials (soon to be published) confirms a small but statistically significant survival benefit. Further large trials addressing this important question are currently under way.

Future trials must attempt to identify predictive factors for response to chemotherapy to enable more selective treatment to be delivered. These could include both clinical and biological parameters, e.g. *K-RAS*. Meanwhile, clinicians must continue to use common sense; palliative chemotherapy is unlikely to be appropriate for frail or chronically ill patients with low performance status, but for selected patients, there is now good evidence of palliative benefit with a small survival prolongation.

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Chemotherapy in Head and Neck Cancer

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HEAD AND neck cancers include all squamous cell carcinomas that originate in the anatomical region comprising the oral cavity, pharynx and larynx and are estimated to be one of the most prevalent tumours in the world. The standard treatment is usually surgery alone and/or radiotherapy. Despite the use of optimal therapy, 50% of patients develop local recurrences and 30% metastatic disease. The overall survival rate is 40% for complete resection and only 20% for unresectable disease [1].

Treatment for local recurrence of metastatic disease is often chemotherapy, even if its efficacy is low. Less than 40% of patients achieve a response, generally of short duration (average 6 months) and median survival is 6–10 months [1].

Response rates with single agents are often variable because patient groups are heterogeneous. Six drugs have demonstrated a high level of activity: methotrexate, cisplatin, carboplatin, 5-fluorouracil (5FU), bleomycin and ifosfamide [2–5].

Methotrexate has been used as a single agent with 40–60 mg/m^2. High doses have not demonstrated any advantages (randomised trial of Southeastern Cancer Study Group with 500 mg/m^2) [3]. Cisplatin, with an average response rate of 28%

Table 1. Single agent activity in head and neck cancer

Agent [Ref.]	Dose (mg/m²)	No. of patients	CR + PR (%)
5FU [3]	400–450	118	15
B [3]	15	347	21
CDDP [3]	100	288	28
CDBCA [4]	350	169	22
DX [18]	60–75	23	18
THP [19]	60	24	28

5FU, fluorouracil; B, bleomycin; CDDP, cisplatin; CBDCA, carboplatin; DX, doxorubicin; THP, pirarubicin.

(range 14–41%) is the most interesting agent. No difference was observed in responses or survival when standard and high doses were compared [3]. Carboplatin (average 26%, range 14–30%) has been actively tested in head and neck cancer because renal, gastrointestinal and neurological toxicity are significantly reduced [4]. The interest in bleomycin is its limited toxicity (no significant myelosuppression) so it can be given at a full dose in combination (Table 1).

Initial studies with 5FU demonstrated only a 15% response rate, but it was initially given as second or third line chemotherapy. Randomised trials have demonstrated that continuous infusion (96 or 120 h) is more efficient or modulators such as leucovorin. A new, more interesting schedule is ifosfamide, administered at 3500 mg/m² on days 1–5, with 43% of responses lasting 11 months. New drugs (paclitaxel, docetaxel) have not provided any additional benefit and responses are short (2 and 5 months, respectively) [6, 7] (Table 2).

To improve response and overall survival, combination therapy, especially with cisplatin and 5FU, has been tested [1, 3]. A randomised trial compared 5FU, cisplatin and their combinations. Although a relatively high response rate was achieved (32% versus 13 and 17%), there was no difference in survival (average 5, 7 months). A combination of three or four agents in addition to cisplatin, 5FU (vindesine, vincristine, bleomycin) did not increase results [8].

The important point of using chemotherapy in metastatic disease is to consider the quality of life. A selected population can be included in a phase II trial and prognostic factors such as a performance status, initial presentation and interval between initial treatment and recurrence need to be integrated.

Because one third of patients present with locally advanced disease, many authors have recourse to neoadjuvant chemotherapy. The aim of first line systemic treatment is to increase local control, overall survival and organ preservation. There are potential advantages to chemotherapy before local treatment: drug diffusion is optimal because the blood supply of the tumour is undisturbed; it is easier to assess the response rate and the performance status is often better (Table 3).

In the 1970s, induction regimens were tested, most of which used cisplatin, bleomycin or methotrexate with acceptable acute toxicity and without an increase morbidity due to local treatment. The overall response rate ranged from 50 to 70% with 20% of complete responses (9–11). Phase II trials have demonstrated that the most effective combination included cisplatin. Two cycles of chemotherapy seem necessary, and half of the clinical responses were correlated with pathological complete responses and an increase in survival. From 1985 to 1994, 25 randomised trials [1, 9–14] compared local treatment with or without neoadjuvant chemotherapy. None have afforded a survival benefit, however, chemotherapy was not used optimally, and the series were small and heterogeneous. Nevertheless, several issues were resolved: the same population responsed to chemotherapy and radiotherapy, thus cure was attainable with organ preservation and a low number of metastases were observed in the chemotherapy group (Table 4).

The T, N, initial tumour site and the chemotherapy regimen are prognostic factors for treatment response and for overall survival. New drugs, high doses or biological modulators have been tested without any real benefit (Table 5).

In conclusion, only a selected population seems to be cured using this approach, with a better quality of life, especially in larynx carcinoma.

Approximately 20% of patients with advanced disease will develop detectable metastases. In trials of adjuvant treatment, only disease-free survival is prolonged in the high risk population with extra-capsular lymph node involvement. The randomised trials have not demonstrated a survival benefit but compliance of treatment is low [10] (Table 6).

Since both neoadjuvant and adjuvant chemotherapy have failed to improve overall survival significantly, one of the current strategies is the concomitant administration of chemotherapy with radiotherapy. The rationale for this approach is based on differences in activity and toxicity with these two modalities. Chemotherapy is expected to potentiate radiotherapy by inhibiting the repair of sublethal lesions, hypoxic cells and cellular synchronisation. All the drugs with recognised activity in head and neck cancer have been tested. Most of the randomised trials with single agents have not achieved a longer survival despite a high response rate, better local control and longer

Table 2. New agents in head and neck cancer chemotherapy

Drug [Ref.]	Dose (mg/m²)	No. of patients	CR + PR (%)	Duration (months)
IFX [5]	3500*	28	43	11
Paclitaxel [6]	250	27	25	2
Docetaxel [20]	100	14	35	5
10-EDAM [21]	80	15	24	1.4

* Ifosfamide 3.5 g/m² d1–d5. IFX, ifosfamide; 10-EDAM, 10 ethyl deaza-aminopterin.

Table 3. Pilot trials of neoadjuvant chemotherapy

Author [Ref.]	Regimen	No. of cycles	No. of patients	CR	CR + PR
Randolph [22]	C + B	2	21	19	71
Hong [23]	C + B	2	40	30	76
Spaulding [24]	C + V + B	2	48	22	88
Elias [9]	C + B + M	1	22	18	73
Price [25]	V + B + M SFU + HyD	2	91		64

C, cisplatin; B, bleomycin; V, vincristine; M; methotrexate; 5FU, 5-fluorouracil; HyD, hydrocortisone.

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Table 4. Randomised trials of neoadjuvant chemotherapy and surgery

Author [Ref.]	Regimen	No. of patients	CR + PR (%)	Survival benefit
Stolwijik [10]	VBMCF	58	NR	None
Taylor [11]	ML	82	6 + 34	None
Rentscheler [26]	M	55	NR	None
HN Contracts [12]	PB	443	3 + 34	None
Kun [27]	BCMF	83	5 + 63	None
Toohil [29]	PF	60	19 + 66	None
Richard [13]	VB (IA)	222	6 + 42	Yes
Martin [29]	PFBM	107	6 + 43	None
Schuller [30]	PBMV	158	19 + 51	None
Martin [29]	PF	75	46 + 22	None
Paccagnella [31]	PF	237	44	None
VA Study [14]	PF	332	49 + 49	None

P, cisplatin; M, methotrexate; V, vincristine; C, cyclophosphamide; F, 5-fluorouracil; L, leucovorin; B, bleomycin.

Table 5. New optimal neoadjuvant regimens

Author [Ref.]	Regimen	No. of patients	CR (%)	CR + PR (%)
Decker [39]	C, 5-FU	35	63	94
Schuller [40]	C, V, M	58	28	66
Ervin [41]	C, B, M	114	26	78
Ensley [42]	C, 5-FU, M, 5-FU	46	46	65
Greemberg [43]	C, 5-FU	30	50	100
Kish [44]	C, 5-FU	11	45	90
Haines [45]	C, B	51	24	69
Dreyfuss [46]	C, 5-FU, LV	35	66	80
Vokes [47]	C, 5-FU, LV	31	29	84

C, cisplatin; 5FU, 5-fluorouracil; V, vincristine, M, methotrexate; LV, leucovorin; B, bleomycin.

Table 6. Adjuvant chemotherapy in head and neck cancer

Investigator [Ref.]	No. of patients	Regimen	Survival
Rentscheler [26]	60	MTX	NS
HNC [12]	462	CP	NS
Taylor [11]	95	MTX/CP + DX	NS
Szpirglas [37]	95	MTX, BLEO	NS
Rossi* [48]	224	DX, C, V	NS
Ervin [41]	46	CP, BLEO, MTX	NS

*Undifferentiated Nasopharyngeal Carcinoma.
MTX, methotrexate; CP, cisplatin; DX, doxorubicin; BLEO, bleomycin; V, vincristine; C, cyclophosphamide.

disease-free survival [15–17]. Different chemotherapy regimens and radiotherapy schedules (accelerated and/or hyperfractionated) have only been tested in Phase II studies. Results indicate higher toxicity requiring hospitalisation and enteral nutrition which could be responsible for the toxicity-related deaths. The management of toxicity is an important parameter when developing these promising but aggressive treatments in patients who are very vulnerable because of considerable intercurrent disease. Four randomised trials have tested sequential treatment versus standard therapy or neoadjuvant chemotherapy followed by standard treatment. Results show a survival benefit in favour of sequential treatment [1, 15–17] (Table 7).

Table 7. Randomised trials of sequential chemotherapy plus radiotherapy versus radiotherapy alone

Author [Ref.]	Regimen	No. of patients	Survival benefit
Von Essen [32]	MTX 5-FU IUDR	87	None
Knowlton [33]	MTX	96	None
Lustig [34]	MTX	75	None
Fazekas [35]	MTX	638	None
Petrovich [15]	VM	23	None
Stell [16]	VMBFHyL	80	None
Shetty [36]	VBMFC	42	None
Szpirglas [37]	DOBP	114	None
Jaulery [38]	PBVM	100	None
Merlano [17]	P + 5FU alt RDT	150	Yes

MTX, methotrexate; F, 5-FU; fluorouracil; IUDR, iododeoxyuridine; V, vincristine; B, bleomycin; C, cyclophosphamide; D, doxorubicin; O, oncovin; P, cisplatin; IA, intraarterial; alt RDT, alternating radiotherapy; HyL, hydrocortisone + folinic acid.

In conclusion, chemotherapy is considered to have a limited role in terms of survival in head and neck cancer. New agents should improve the outcome of patients with metastatic disease, and then be developed in neoadjuvant trials. Identification of populations at high risk for local relapse or distant metastasis will make it easier to tailor treatment, simultaneous chemoradiotherapy and neoadjuvant chemotherapy, respectively, for these different forms of the disease.

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