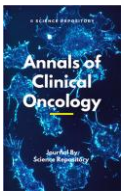

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Research Article

Induction Chemotherapy with Docetaxel, Cisplatin and 5-Fluorouracil (TPF) Followed by Chemoradiotherapy for Locally Advanced Head and Neck Cancer: Can It Achieve Its Potential?

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ARTICLE INFO

Article history:
Received: 26 August, 2020
Accepted: 9 September, 2020
Published: 28 September, 2020

Keywords:
Head and neck cancer
induction chemotherapy
docetaxel
chemoradiotherapy
dose intensity

ABSTRACT

Objective: In view of concerns about toxicity and deliverability of induction chemotherapy and its impact on subsequent chemoradiotherapy, a retrospective review was carried out with patients treated for locally advanced head and neck cancer (LAHNC) in a single centre between 2007-2017.

Patients and Interventions: Patients with LAHNC and good performance status receiving induction chemotherapy with docetaxel, cisplatin and 5-fluorouracil (TPF) followed by chemoradiotherapy to 70Gy in 35 daily fractions with platinum-based chemotherapy.

Main Outcome Measures: Overall and cause-specific survival, rates of locoregional recurrence or distant metastasis, treatment-related toxicity.

Results: One hundred and eight patients with LAHNC were treated with 1-4 cycles of TPF (95 receiving two cycles) followed by chemoradiotherapy. The mean delivered dose intensity was 97.6% for all TPF cycles. Median interval from the start of the final cycle of TPF to the start of radiotherapy was 24 days, with 92/103 (89%) starting radiotherapy within 28 days. Median radiation treatment time was 47 days. The mean delivered dose intensity for chemotherapy delivered concurrently with radiotherapy was 97%. There were significantly fewer dose reductions in those receiving platinum/5FU combinations than platinum only regimes ($P < 0.0001$). For those receiving two cycles of TPF, 90% of patients completed the whole course of treatment within 14 weeks (median overall treatment time 13.1 weeks). There were four treatment-related deaths during induction chemotherapy and none during radiotherapy. Twenty-five developed locoregional failure and 13 distant metastases (both in eight). Actuarial overall survival was 60.7% at five years, with progression-free survival of 77.9% at two years and 74.1% at five years. For oropharynx cancers, overall survival was 70.4% and progression-free survival 80.8% at five years.

Conclusion: Although significant toxicity from TPF was observed, with appropriate support, it is possible to complete treatment without undue compromise of subsequent treatment.

Introduction

In the search for more effective treatments for locally advanced head and neck cancer (LAHNC), there has been a steady increase in treatment intensity. The use of induction chemotherapy can produce higher response rates but translating that into improvements in survival has proven more difficult [1]. A meta-analysis of randomized trials conducted between 1965 and 2000 showed a small but not statistically significant survival benefit (2.3% at 5 years) from the addition of induction chemotherapy to locoregional treatment with radiotherapy or

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http://dx.doi.org/10.31487/j.ACO.2020.02.04

chemoradiotherapy (LRT) [2]. With the subsequent development of taxanes, particularly docetaxel, several randomized trials compared the combination of cisplatin and 5-fluorouracil (5FU; PF) with the same drugs plus docetaxel (TPF) prior to LRT. In a meta-analysis of five trials (1772 patients), TPF induction produced a 7.4% improvement in overall survival at five years [3].

However, the regimes compared were not simply cisplatin/5FU ± docetaxel as the cisplatin and 5FU doses were higher in the PF regime (although TPF in the TAX 324 trial contained 100 mg/m^2 cisplatin), and the regime in one trial contained paclitaxel, not docetaxel [4, 5]. A subsequent meta-analysis of six trials (1280 patients) of LRT with or without TPF induction found, somewhat paradoxically, no survival advantage with TPF induction, although significant improvement in overall and progression-free survival was seen in non-oropharyngeal cancers [6]. The reasons for TPF being more effective than PF, yet no more effective than LRT alone, merits further scrutiny. Although induction chemotherapy reduces the risk of distant metastases, given their relatively low incidence in LAHNC, survival is mostly determined by locoregional control [6, 7].

In two of the earliest trials of LRT with or without induction chemotherapy, there was a 2.9 times greater risk of persistent or recurrent disease in the chemotherapy arms of both trials (equivalent to a 12-23% difference in overall survival at 19-24 months), which the investigators attributed to delays in starting definitive treatment [8]. In the EORTC 24971/TAX 323 study, there was a median interval between chemotherapy and starting radiotherapy of 5.3 and 5.7 weeks in the PF and TPF arms respectively (the protocol allowing up to seven weeks) and in the GORTEC 2000-01 study, this interval was 50 days, representing an average treatment extension of 2.3-4.1 weeks [1, 9].

In the TPF versus PF studies, the median radiation treatment time (RTT) was 7.1 weeks in the trials where concomitant carboplatin or no concomitant chemotherapy was given, and over eight weeks when cisplatin was given [4, 9-11]. In the TAX 324 study, those in the upper quartile with an overall treatment time of more than 21.3 weeks or in the upper quartile with an RTT in excess of 8 weeks (regardless of allocated treatment) had statistically worse overall survival [12]. In the same trial, there were significantly more treatment delays during PF (65%) than during TPF (29%) and 25% and 21% of those receiving PF and TPF respectively, did not complete chemoradiotherapy [4].

In the meta-analysis of trials of LRT ± TPF induction, 27% of patients in the TPF arms failed to complete chemoradiotherapy compared to 16% in the control arms (relative risk 1.3; $P < 0.001$) [6]. In the TTCC trial, 36% of patients in the TPF arm received less than 95% of the planned radiation dose compared to 30% in the PF arm and 29% who received chemoradiotherapy alone [11]. In the CONDOR trial, giving up to four cycles of TPF prior to randomization between different chemoradiotherapy options, only 22% of the conventional radiotherapy arm were able to receive all three doses of concomitant cisplatin [13]. In the TREMPLIN trial, after three cycles of TPF, only 45% in the chemoradiotherapy with cisplatin arm received cisplatin in full dosage [14]. In the TTCC trial, 41% of TPF patients and 31% of PF patients received less than three cycles of cisplatin during radiotherapy compared to 19% in the chemoradiotherapy alone arm [11]. In a review of treatment toxicity of TPF induction in nine studies of non-nasopharyngeal cancers, only three reported the median interval between TPF and LRT (range 22-31 days) and only three reported the proportion receiving a cumulative cisplatin dose of at least 200mg/m^2 during radiotherapy (range 66-85%) [15]. Deaths attributable to TPF and PF in randomized trials were 0.4-3.9% (14/695, 2.0%) and 0.4-1.9% (15/686, 2.2%) respectively [4, 9-11]. In a trial of LRT ± TPF induction, mortality during TPF was 10% and as a result the trial stopped early [16]. In non-randomized studies, deaths during TPF were reported in 0-14% [17-20].

Laryngectomy-free survival was higher with TPF than PF (52-74% versus 32-58%) in two trials of cancers of the larynx and hypopharynx with improvement in overall survival in one but not the other [4, 10]. Larynx dysfunction-free survival (i.e. without tracheostomy or feeding tube) was higher in the TPF arm (67% versus 46%) [10]. In a retrospective series of 70 patients with $T_{2\text{-}4}$ cancers of the larynx and hypopharynx treated with a median three cycles of TPF followed by LRT, larynx preservation at three months was 89.6% [21]. Though there is a reluctance to consider larynx preservation for T4 cancers with cartilage invasion, a proportion of these patients are suitable for this approach with good effect [22, 23].

In summary, treatment delivery in patients treated with PF or TPF in randomized trials has been less than optimal and accompanied by incomplete reporting of treatment details. Delays and dose reductions of TPF and chemoradiotherapy might all reduce the effectiveness of treatment. If these consequences can be minimised, it remains possible that TPF induction might yet prove superior to chemoradiotherapy alone in LAHNC.

Materials and Methods

Patients with LAHNC (excluding nasopharyngeal and sinonasal primaries) were considered for TPF induction chemotherapy if, in general, they were of excellent performance status (WHO PS0) and age under 70, with tumors staged as T4 and/or N3, or of sufficient tumor bulk (in the opinion of the multidisciplinary team) to warrant induction chemotherapy or where this might offer a greater possibility of organ preservation. All patients diagnosed between March 2007 and November 2017 and referred to a single clinical oncologist are included.

TPF consisted of docetaxel 75mg/m^2 and cisplatin 75mg/m^2 (with steroid premedication, hydration and antiemetics), followed by continuous infusion of 5FU 750mg/m^2 daily over five days via an indwelling line. Prophylactic filgrastim (G-CSF) was given to all but the first four patients. In general, two cycles of TPF were planned. In some cases, a third was given to allow for assessment of treatment response after two cycles (to allow possible surgery for poor responders) without creating a 'gap' between TPF and chemoradiotherapy.

Radiotherapy was planned to start approximately three weeks following the first day of the final cycle of TPF. The first 46 patients between 2007-2012 were treated with 3D-conformal radiotherapy (3DCRT) and subsequent patients treated with volumetric arc therapy (IMRT; RapidArc, Varian Medical Systems) to a prescribed dose of 70Gy in 35 daily fractions over seven weeks starting on a Monday to minimise RTT. Patients received concurrent chemotherapy with cisplatin 75mg/m^2 and

5-fluorouracil 750mg/m^2 daily over four days by continuous infusion in the first and fifth weeks. From 2014, three-weekly cisplatin 100mg/m^2 was used for cancers in non-oropharynx sites. Carboplatin (AUC=5) was substituted for cisplatin in the presence of tinnitus, hearing loss, renal impairment or reduced PS. Cetuximab was given in place of platinum-based chemotherapy following a poor response to TPF (i.e. disease stabilisation or progression).

All patients were supported by a specialist team comprising dietician, speech and language therapist, radiographers and nurses. Percutaneous endoscopic gastrostomy (PEG) insertion was recommended prior to radiotherapy. Morbidity was assessed retrospectively by case note review. Tumor response following treatment completion was assessed by nasoendoscopy and neck palpation at regular intervals and, since 2013, by additional PET/CT. Dose intensity was calculated as the percentage of protocol dose (in mg/m^2) for each drug delivered in each cycle and assuming each drug contributed equally to the effectiveness of treatment. Actuarial survival was calculated using the Kaplan-Meier method (StatsDirect version 3.2.7, Cambridge, UK).

Results

I Treatment Delivery

One hundred and eight patients (93 men, 15 women) of median age 57 years (range 35-75) were treated (Table 1). Oropharynx was the commonest tumor site (72%), followed by larynx and hypopharynx (20%; Table 1). All but two were PS0 and all but four had no or minimal comorbidity as assessed by the ACE-27 comorbidity index. Ninety-one (84%) had T4 tumors and 87 (81%) had nodal involvement. Five received a single cycle of TPF, 95 (88%) two cycles, seven a third cycle and one a fourth. Prophylactic G-CSF was given to all but the first four patients, commencing initially on the day following 5FU pump disconnection (i.e. day 6). In May 2010, this changed to day 2 in response to severe neutropenia developing around day 7. The second cycle was delivered after 21 days ± 1 day in 92 (89%). The interval from day 1 of the final TPF cycle to the start of radiotherapy was 21 days or less in 46 (45%) and 22-28 days in a further 46 (median 24 days; Table 2).

Table 1: Patient characteristics.

characteristic		number	total
sex	male		93
	female		15 (16%)
age	30-40		4
	40-49		12
	50-59		50
	60-69		36
	>70		6
	median (range)	57 (35-75)	
WHO performance status	0		106
	1		2
ACE-27 comorbidity index	0		69
	1		35
	2		4
	3		0
primary site	oral cavity *		4 (3.7%)
	oropharynx		78 (72.2%)
	soft palate	2	
	tonsil †	30	
	tongue base	39	
	ant surface epiglottis	1	
	oropharynx unspecified	6	
	hypopharynx		8 (7.4%)
	pyriform fossa	4	
	postcricoid	2	
	hypopharynx unspecified	2	
	larynx		14 (13.0%)
	supraglottis	2	
	glottis	12	
	unknown primary		4 (3.7%)
histology	squamous		98
	basaloid squamous		8
	adenosquamous		1
	undifferentiated		1
grade	well differentiated		2
	moderately differentiated		43

	poorly differentiated	60
	undifferentiated	1
	not graded	2
tumour stage	T0-3	17
	T4	91 (84%)
nodal involvement	N0	21
	N1	11
	N2	63 (58%)
	N3	13
P16	positive	33
	negative	12
	unknown	63

* includes one patient with recurrent floor of mouth cancer.

† includes two patients with a previously treated tonsillar cancer in the same area 10 and 12 years previously.

Table 2: Chemotherapy details.

characteristic		**number**
interval between first and second cycles *	20-22 days	92
	23-28 days	10
	≥29 days	1
	median (range)	21 (20-32)
interval between second and third cycles *	20-22 days	5
	23-28 days	3
	≥29 days	0
	median (range)	21 (21-28)
interval between final cycle and start of radiotherapy *	18-21days	46
	22-28 days	46
	≥29 days	11 [3]
	median (range)	24 (18-83)
concurrent chemotherapy	cisplatin + 5FU	77
	carboplatin + 5FU	1
	cisplatin only	15
	cisplatin / carboplatin	4
	carboplatin only	2
	cetuximab	3
	none	1
overall treatment time †‡	two cycles TPF: median (range)	13.1 (11.1-21.6)
	three cycles TPF: median (range)	17.7 (15.3-21.3)
dose intensity: first cycle	mean	99.2
	median (range)	100 (80-100)
	number with dose reduction §	8 (7.4%)
	number with ≥90% dose intensity	104 (96.3%)
dose intensity: second cycle	mean	96.0
	median (range)	100 (67-100)
	number with dose reduction	19 (18.9%)
	number with ≥90% dose intensity	87 (86.1%)
dose intensity: third cycle	mean	97.1
	median (range)	100 (80-100)
	number with dose reduction	1 (14.3%)
	number with ≥90% dose intensity	6 (85.7%)
mean dose intensity (all TPF cycles)	mean	97.6
	median (range)	100 (80-100)
	number receiving full dose throughout	85 (80.2%)
	number with ≥90% dose intensity	94 (88.7%)
dose intensity: concurrent chemotherapy	number with dose reduction week 1	4/99
	number with dose reduction week 4/5	12/99
	number with dose reduction week 7	11/21

mean dose intensity (2-3 cycles concurrent chemotherapy)	mean	97.1
	median (range)	100 (67-100)
	number receiving full dose throughout	87 (85.3%)
	number with ≥90% mean dose intensity	91 (89.2%)

*: calculated by subtracting the relevant dates.

†: calculated as the number of days including the first and last (i.e. subtracting the relevant dates plus one).

‡: includes two patients presenting with recurrent disease having surgery between TPF and radiotherapy (61 and 68 days), one patient having radiofrequency ablation for a solitary liver metastasis prior to radiotherapy (55 days) and a further patient referred elsewhere for assessment of resectability prior to radiotherapy (83 days).

§: The first three patients received 5FU infusion over four days rather than five (dose intensity calculated as 93%).

One hundred and three patients completed radiotherapy. Ninety-five (92%) received 70Gy in 35 fractions with 86 (91%) completing treatment in 46-47 days. Two previously irradiated patients received a planned dose of 60Gy, two with a complete clinical response to TPF received 66Gy and one with the resistant recurrent nodal disease treated to 76Gy. Only two with resistant disease and declining PS received less than the intended dose. Median overall treatment time (i.e. from the first day of chemotherapy to the final day of radiotherapy) was 13.1 weeks (range 11.1-21.6) in those receiving two cycles of TPF and 17.7 weeks (range 15.3-21.3) in those receiving three cycles (Table 2). Ninety per cent of patients receiving two cycles completed treatment within 14 weeks (i.e. within one week of the scheduled duration). Seventy-eight patients (76%) commenced concurrent chemotherapy with a platinum/5FU combination, with carboplatin (AUC=5) substituted for cisplatin for one or both cycles in three, and 5FU omitted from the second cycle in one (Table 2). Twenty-one (20%) received concurrent chemotherapy with single-agent cisplatin or carboplatin, with three subsequently switching to carboplatin. Three received weekly cetuximab, and one received no concurrent treatment.

Dose intensity averaged across the two or three planned cycles (excluding those receiving cetuximab) is shown in (Table 2). Over all there were 4/99, 12/99 and 11/21 patients with dose reductions after the first, second and (where applicable) third cycles of concurrent chemotherapy. In patients receiving platinum/5FU combinations, only 3/78 (4%) had dose reductions in week 5 but in the platinum only regimes, 9/21 (43%) had dose reductions in week 4 and 11/21 (52%) in week 7. At least 90% dose intensity was achieved in 76/78 (97%) of those receiving platinum/5FU combinations compared to 12/21 (57%) of those receiving single-agent platinum (unpaired t-test, $P < 0.0001$). In the platinum-only group, all received at least 200mg/m^2 cisplatin (or equivalent).

II Toxicity

Full details of toxicity were available for all but eight patients after the first cycle but for less than half following subsequent cycles. Following the first cycle, diarrhoea at any time was reported by 78% and mucositis by 48% (Table 3). There were two instances of 5FU-related chest pain, diagnosed as myocardial infarction in one. Seven developed line-related thrombosis, one an arm vein thrombosis subsequent to line removal and one a leg vein thrombosis. Forty-two patients required in-patient admission after the first cycle (39%; 312 in-patient days, median length of stay six days) and 21 after the second cycle (20%; 158 in-patient days, median length of stay four days). Infection was the comment reason for admission (Table 3). Twenty-six patients required admission during radiotherapy.

Table 3: Treatment toxicity and hospital admission following TPF chemotherapy.

Treatment toxicity, incidence and duration, reported following the first cycle of TPF. Admissions to hospital by length of stay and including the commonest causes for admission.

toxicity		**number evaluable**	**number with toxicity (%)**
neutropenia *	neutrophils ≤1.5	99	21
	neutrophils ≤1.0		20
diarrhoea *	none	103	23
	at any time		80 (78)
	lasting 1-3 days	58	31
	lasting 4-7 days		20
	lasting 8-10 days		5
	lasting 11-14 days		2
mucositis *	none	100	52
	at any time		48 (48)
	lasting 1-3 days	23	6
	lasting 4-7 days		12
	lasting 8-10 days		3
	lasting 11-14 days		2
in-patient admission	patients admitted	108	42 (39)
(first cycle)	admitted 1-3 days		11
	admitted 4-7 days		16

	admitted 8-14 days		7
	admitted ≥15 days		6
	neutropenic sepsis		17
	infection (non-neutropenic)		8
	diarrhoea †		8
in-patient admission (second cycle)	patients admitted	103	21 (20)
	admitted 1-3 days		8
	admitted 4-7 days		5
	admitted 8-14 days		5
	admitted ≥15 days		3
	neutropenic sepsis		1
	infection (non-neutropenic)		7
	diarrhoea ‡		3

*: toxicity following the first cycle only.

†: includes two patients with diarrhoea due to Campylobacter and one with Clostridium difficile.

‡: includes one patient with diarrhoea due to Clostridium difficile.

III Survival and Recurrence

There were 42 deaths, with 25 from head and neck cancer (Table 4). There were five deaths during TPF chemotherapy (four from infection and one from disease progression) and none during radiotherapy. Four deaths, all due to cancer, occurred within 90 days of treatment completion. Deaths from cancer occurred 2.6-85.6 (median 10.9) months from diagnosis, with 80% occurring within 24 months. Median follow-up of surviving patients was 53 months (range 13-118). For the whole group, actuarial overall survival was 70.2% at two years and 60.7% at five years, and cancer-specific survival 75.2% at two years and 69.9% at five years. Patients with oropharynx cancers had better overall survival at five years than those with larynx and hypopharynx cancer (70.4%, 62.5% and 50% respectively) (Figure 1). Cancer-specific survival at five years was 74.3% for oropharynx, 78.6% for larynx and 50% for hypopharynx cancers (Figure 2). Four-year overall survival of oropharynx cancers diagnosed between 2007-2010 was 58.0%, between 2011-2014, 74.8% and between 2015-2017, 83.3%. P16-positive cancers had better five-year overall survival than those which were P16-negative or P16-unknown (72.6%, 66.7% and 55.4% respectively).

Table 4: Deaths and late complications following treatment.

	cause	**number**
deaths during treatment	neutropenic sepsis	3
	pneumonia	1
	disease progression and Guillain-Barré syndrome	1
deaths following treatment	head & neck cancer	25
	non-small cell lung cancer	1
	infection	2
	COPD	1
	drug overdose	1
	pharyngeal haemorrhage	1
	cerebral haemorrhage	1
	progressive supranuclear palsy	1
	unknown	4
late complications (non-fatal)	tinnitus or hearing loss	8
	neuropathy	4
	cognitive deficit	1
	osteoradionecrosis	4
	trismus	4
	pharyngeal bleed (without recurrence)	1
	oesophageal stricture	1
	oedema or lymphoedema	4
second cancer (non-fatal)	prostate	4

In those completing chemoradiotherapy, 25/103 (24.3 %) suffered disease progression. Thirteen (12.6%) developed distant metastases (eight with locoregional recurrence). There were 20 with locoregional progression (seven at or adjacent to the primary site, nine in the neck, two at the skull base and two both adjacent to the primary site and in the neck). Median time to progression was 8.5 months (range 3.6-40.9). Actuarial progression-free survival for the whole group was 77.9% at two years and 74.1% at five years and for oropharynx cancers, 82.9% at two years and 80.8% at five years (Figure 3). Median survival following

progression was 4.1 months (range 0-67), with only 4/25 (16%) surviving beyond 12 months.

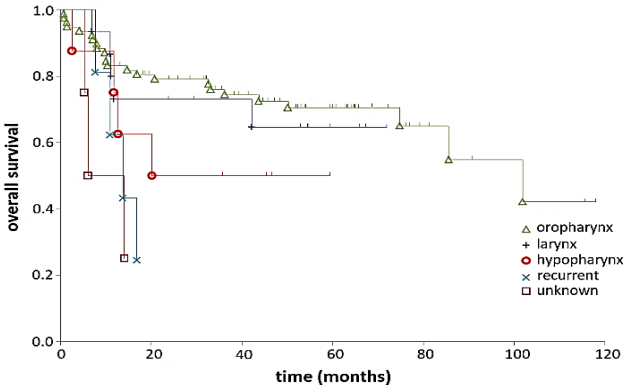

Figure 1: Actuarial overall survival.

Actuarial overall survival calculated for all 108 patients, in subgroups by tumor site.

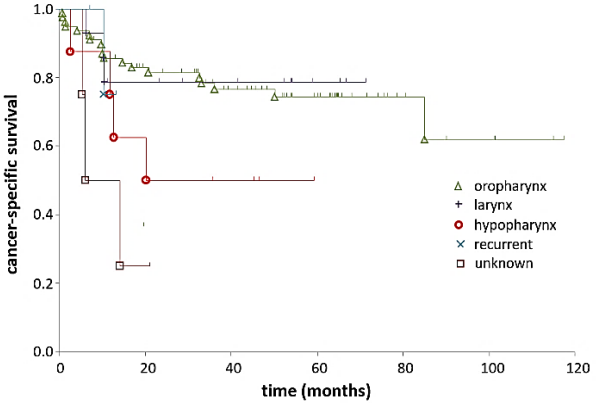

Figure 2: Cancer-specific survival.

Actuarial cancer-specific survival for all 108 patients, in subgroups by tumor site. Deaths during treatment from infective causes are included in cancer deaths, one later death from a pharyngeal bleed is also classified as a cancer death.

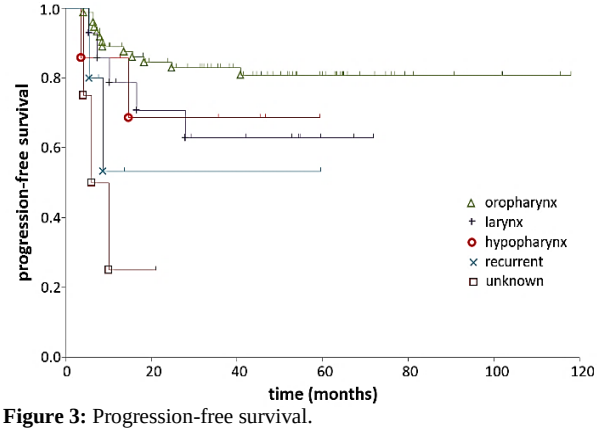

Figure 3: Progression-free survival.

Actuarial progression-free survival for 103 patients, in subgroups by tumor site. Five patients who died before starting radiotherapy are excluded. Progression includes both distant metastases and locoregional recurrence.

IV Larynx Preservation

One patient with hypopharynx cancer and Guillain-Barré syndrome died from progressive cancer and did not receive radiotherapy. Of the 21 remaining patients with larynx or hypopharynx cancers, two developed distant metastases, one both distant metastasis and locoregional recurrence, and four locoregional recurrences. One patient underwent neck dissection and subsequent total laryngectomy. The other recurrences (in the absence of distant metastasis) were unresectable. Actuarial progression-free survival at five years was 62.9% for larynx cancers and 68.6% for hypopharynx cancers (Figure 3).

With respect to laryngeal function, 4/21 patients had PEG tubes at the time of death (two dying from progressive cancer, two from unknown causes). Of currently surviving patients, one had a laryngectomy, two have tracheostomy tubes, one of whom also has a PEG tube. Actuarial larynx dysfunction-free survival (i.e. without tracheostomy or PEG tube) was 73.1% at five years.

V Late Complications of Treatment

Late complications of treatment (Table 4) included four cases of mandibular osteoradionecrosis in the group treated by 3DCRT but none after IMRT (P=0.04; Fisher's exact test). There were four cases of oedema after IMRT but none after 3DCRT (P=0.12).

Ninety-nine patients underwent PEG insertion prior to treatment. One patient was PEG-dependent following a previous oral cancer, and twenty PEGs remained *in situ* at the time of death. One PEG tube was later reinserted. In survivors, PEG tubes have removed a median of 5.0 months (range 1.1-32.9) post-radiotherapy, with an actuarial risk of a PEG remaining *in situ* of 14.4% at 12 months and 1.8% at 24 months (Figure 4). Two surviving patients (with tongue base and larynx cancers) had PEG tubes and tracheostomies at last follow-up.

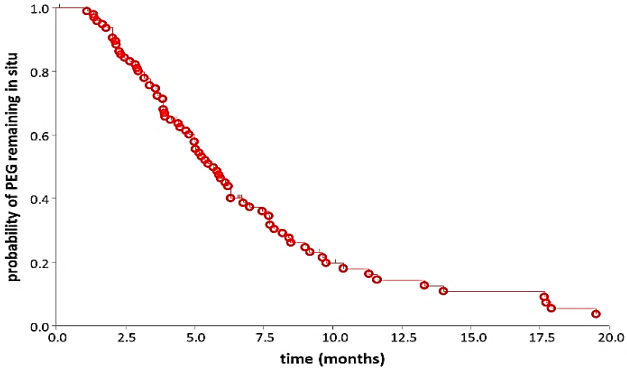

Figure 4: Time to PEG removal.

Actuarial risk of gastrostomy (PEG) tubes remaining *in situ* for 97 patients who completed radiotherapy. Two patients who died prior to starting radiotherapy are excluded. Time to PEG removal is calculated from the final day of radiotherapy.

Discussion

In contrast to randomized trial evidence, this retrospective case series shows that induction chemotherapy with two cycles of TPF is

deliverable with at least 90% of patients commencing radiotherapy within four weeks of the final cycle of TPF, receiving the planned dose of 70Gy and completing treatment within one week of the planned duration. Ninety-seven per cent of those treated with a platinum/5FU combination received at least 90% of the planned dose compared to 57% of those with a platinum-only regime. In this series, patient selection focused on those with PS0 in contrast to trials in which 56% of patients were PS1 [3]. In the TAX 324 trial (where 42% were PS1), five-year survival was 62% in those with PS0 and 44% with PS1 (P=0.002) [12]. In a retrospective study of patients with lower socioeconomic status and median Karnofsky PS of 80, there was higher treatment mortality in those with KPS < 80 [18]. PS was a significant prognostic indicator in one retrospective study but not in another, and local control and survival were reduced in patients with a higher Charlson comorbidity index [19, 20, 24].

In randomized trials, three cycles of TPF induction have been the norm but in a retrospective study of 71 patients, there were more radiotherapy treatment breaks and poorer local control and survival in those who had three as opposed to two cycles [24]. In one randomized trial using two cycles of TPF (and a planned gap of just four weeks between TPF and chemoradiotherapy), there was less impact on radiation dose (reduced in 19% versus 13% after chemoradiotherapy alone) and no difference in concomitant cisplatin dose [16]. Higher rates of response and of survival were seen in the TPF arm, though not reaching statistical significance. Prophylactic G-CSF, not permitted in several trials, is essential to reduce the risk of neutropenic sepsis and death following TPF [1, 4, 9, 11, 16]. Timing is also critical, with fewer deaths, less febrile neutropenia and fewer delays to subsequent TPF seen in a group receiving G-CSF on day three rather than day seven [21].

Concomitant cisplatin is generally considered the standard of care and evidence suggests that higher cumulative doses (not limited to a 'threshold' dose of 200mg/m^2) are more effective and best given on a three-weekly basis [25]. In a meta-analysis of radiotherapy with or without concomitant chemotherapy, studies of single-agent chemotherapy with a platin appeared similarly effective to polychemotherapy with a platinum/5FU combination [2]. Although not directly compared, hazard ratios (95% confidence intervals) were similar: 0.74 (0.67-0.82) for platinum monotherapy versus 0.75 (0.67-0.84) for platinum/5FU combinations. With full-dose cisplatin difficult to deliver following TPF induction, and planned doses of cisplatin/5FU more readily achieved as this study demonstrates, cisplatin/5FU should be considered as an alternative. The lower cisplatin dose delivered in combination might potentially reduce the risk of tinnitus and hearing loss [26].

Access to 24-hour support throughout treatment is essential to ensure that acute morbidity is rapidly assessed and treated. In our own experience, this may have contributed to there being three infective deaths between 2007-2011 but only one between 2012-2017, during which time overall survival also improved. Familiarity with the complexities of TPF is clearly important. In three multicentre trials, the 433 patients in the TPF arms were treated across a total of 83 centres [11, 27, 28]. The impact of this relatively small number of cases per centre in respect of treatment familiarity and outcome is uncertain.

Larynx preservation remains a compelling indication for TPF induction chemotherapy. The strong association between response to induction chemotherapy and subsequent response to chemoradiotherapy has encouraged the concept of chemoselection using one or two cycles of TPF to predict those with a higher chance of larynx preservation with a non-surgical approach [29]. The results of the current study, although containing only 22 patients with larynx or hypopharynx cancers, are consistent with the published series. Estimating the potential benefit of optimally delivered TPF induction relative to chemoradiotherapy alone is more difficult. Prolongation of radiotherapy for head and neck cancer results in worse outcomes, equivalent to a decrease in overall survival of 12% at 5 years for those whose radiation treatment time is eight weeks or more compared to those with normal or only slightly prolonged treatment [30]. In a study of 1012 patients undergoing radiotherapy for laryngeal cancer, local control declined by 1.4% for every day of treatment prolongation, equivalent to 10% for a one-week prolongation [31].

Retrospective studies have shown better outcomes in patients receiving cumulative cisplatin doses higher than 200mg/m^2 [32, 33]. Using data from six randomized studies of chemoradiotherapy versus radiotherapy alone, a linear dose-response relationship has been described [25]. This equates to a predicted overall survival benefit (compared to radiotherapy alone) of 10% with a cumulative dose of 175mg/m^2 and 27% with a cumulative dose of 250mg/m^2. For untreated oropharyngeal cancer, there is an overall survival detriment of 2.2% per week of delay in starting radiotherapy [34]. If the rate of tumor regrowth were no faster than prior to TPF, a 7-week gap (i.e. four extra weeks) between TPF and radiotherapy could account for a decrease in survival of around 9%. In practice, this is probably an underestimate as one would expect tumor proliferation to accelerate with time, so that there might be little increase between weeks 3-5 but much more between weeks 5-7.

In summary, delays in starting radiotherapy after TPF might account for a 10% reduction in outcome, increased radiation treatment time 5-10% and concomitant chemotherapy dose reductions a further 5-10%. If TPF induction and subsequent chemoradiotherapy can be delivered with minimal delay or dose reduction, one might hope (in the context of a randomized trial) to see a true benefit from TPF induction.

Conclusion

This series demonstrates that the potential for TPF to compromise chemoradiotherapy delivery can be mitigated by careful case selection and limiting TPF to two cycles. Radiotherapy should commence without delay and include concomitant chemotherapy with three-weekly cisplatin or (preferably) cisplatin/5FU. Future trials should recruit from centres with demonstrable familiarity with TPF and include detailed reporting of treatment timing and doses delivered.

Acknowledgements

The author is grateful to Dr. Andriana Michaelidou for helpful comments.

Competing Interest

None.

Funding

None.

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