

4th FY Khoo Memorial Lecture 2008 Nasopharyngeal Cancer Workgroup – The Past, The Present and The Future

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Introduction

Thank you Madam Chairman. First, I would like to thank the Singapore Radiological Society and the College of Radiologists, Academy of Medicine Singapore for giving me the honor of delivering this the 4th FY Khoo Memorial Lecture, 2008.

Dr Khoo Fun Yong

Dr Khoo Fun Yong, was a radiologist extraordinaire. Besides being the First Asian Head of a Radiology Department in Singapore, he was also the first Asian Head of Radiotherapy, as radiologists in that era practiced both radiodiagnosis as well as radiotherapy. He also had the honor of being the first person in Singapore to report on the radiology of the nasopharynx.¹ Dr Khoo was also a historian, and spent a good part of his retirement, collating the history of radiology in Singapore, which resulted in this monograph – “X-rays in Singapore: 1896 – 1975”

Nasopharyngeal Cancer Workgroup

So following in the same historical vein, I will attempt to recall the history of the Nasopharyngeal Cancer Workgroup of the Department of Radiation Oncology, National Cancer Centre, since its inception, its current activities as well as its plans for the future. On the 18th of January 1992, all the consultants of what was then known as the Department of Therapeutic Radiology, Singapore General Hospital, sat down together to hammer out a common protocol for the treatment of nasopharyngeal cancer (NPC). Since then, all our NPC patients have been treated on standard protocols, which are reviewed at regular intervals. We also worked out a common nomenclature for coding the sites of spread on imaging. We then collaborated with Dr Vincent Chong, from the Department of Diagnostic Radiology, on a trial comparing CT with MRI for the staging of NPC. This resulted in Dr Chong publishing over 40 papers and even more chapters; and he was subsequently also invited to sit on the Head and Neck Expert Panel of the UICC TNM Task Force. He also co-authored a monograph on NPC,² which was the next workgroup initiative. We continue to

actively participate in imaging issues in NPC, and in 2007, we presented a poster at The American Society of Therapeutic Radiology and Oncology (ASTRO) conference comparing CT-PET with PET, CT and conventional imaging for the staging of distant disease in NPC.³

With a common treatment protocol in place, we analysed and published the results of our 1992 to 1994 cohort of patients.⁴ The 5-year overall survival (OS) of this cohort was 58.5% with a 10-year OS of 45.4%; and these results were comparable to results coming from Hong Kong⁵ and the United States.

In 1994, we learnt that the UICC was considering overhauling the whole TNM staging for NPC. We submitted a paper giving our views, and to our surprise received a favourable response from the UICC; and thus began our involvement in TNM staging.⁶ We continue to participate actively in this area, and in 2007, we presented a poster⁷ at The European Society of Therapeutic Radiology and Oncology (ESTRO) conference, supporting a Guangzhou proposal to classify retropharyngeal involvement as “N” disease; an issue, which had previously not been addressed because of imaging difficulties.

In 1996, the department held its retreat at The Singapore Swimming Club. It was a watershed year for us. That year, the department decided that it would go down the path of sub-specialisation. It also decided to launch a pilot Phase II trial in NPC and this would be followed by a Phase III trial.

In 1998, the UICC invited us to host a UICC NPC workshop, which was held at The Singapore International Convention and Exhibition Center at Suntec City. The workshop was a success and we had over 200 participants and over 40 speakers from 15 countries from all over the world.

First Major Advancement in NPC Treatment

At the plenary session of the 1996 American Society of Clinical Oncology (ASCO) conference, Al-Sarraf presented the results of the US Intergroup 00-99 trial⁸ which showed a 25% improvement in overall survival with the addition of

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chemotherapy to radiotherapy (chemo-RT) in patients with locally advanced NPC. I do not think anyone in this room would deny that, this finding represented the first major advancement in the treatment of NPC in the modern era. However, for those of us in the East where NPC is endemic, we had some reservations about applying this finding into routine clinical care. Chan⁹ summarised well our reservations – firstly, about a third of the patients in the 00-99 trial had WHO Type I histology, whereas in the East over 95% of our patients had the endemic form of NPC (i.e. WHO Types III and II). Secondly, the radiotherapy (RT) technique used was less aggressive and the results of the RT alone arm, was inferior to that of historical data for our Singaporean and Hong Kong patients.

However, we could not completely ignore those compelling results either. We thus launched a Phase II trial¹⁰ using the Al-Sarraf regimen on our local patients and found that it was feasible and that we could deliver the full dose of chemotherapy in our Asian patients. You need to understand that in 1997, concurrent chemo-RT was not in vogue and had never been tried locally, and thus we had our reservations to its tolerability.

SQNP01

Following the success of our phase II trial, we proceeded to launch a Phase III Randomized Trial (SQNP01) comparing RT with or without chemotherapy using essentially the Al-Sarraf regimen, but restricted to only patients with the endemic form of NPC. The trial ran from 1997 till 2003, and the early results have been published in the Journal of Clinical Oncology,¹¹ and presented at ASCO in 2004 and at ASTRO in 2006.

In essence, patients with Stage III and IV NPC with WHO Types 2 and 3 histology only, were randomised to

receive RT to 70Gy in 35 fractions versus the same RT with concurrent cisplatin during weeks 1,4 and 7 of RT and followed with 3 cycles of adjuvant PF given monthly after the RT phase. A total of 221 patients were randomised, and the latest results, which I will present, are at a median follow-up period of 6.6 years (Figs. 1a-c). Five patients have been lost to follow-up, and all patients are included on an intention-to-treat analysis. The 5-year distant metastases rate was 37% vs. 17% in favour of chemo-RT; the 5 year disease free survival was 46% vs. 59% with a hazard ratio of 0.67 and $P = 0.0318$; and the 5 year overall survival rate was 49% vs. 67% with a hazard ratio of 0.60 and P value of 0.0077 – all in favour of the chemo-RT arm. We thus confirmed the validity of the US 00-99 trial, and also showed that this treatment was applicable to the endemic form of NPC.

Chemo-RT for NPC

To date there are now about 8 randomised trials^{8,11-17} of chemo-RT for NPC (Table 1), and almost all show a benefit with the addition of chemotherapy, and we can safely say

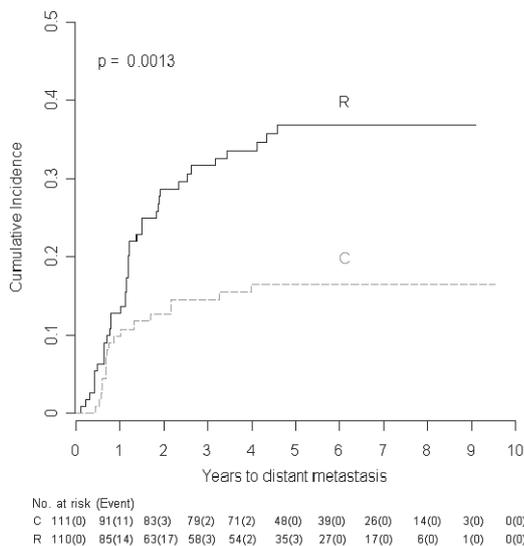


Fig. 1a. SQNP01: Five-year distant metastases rate.

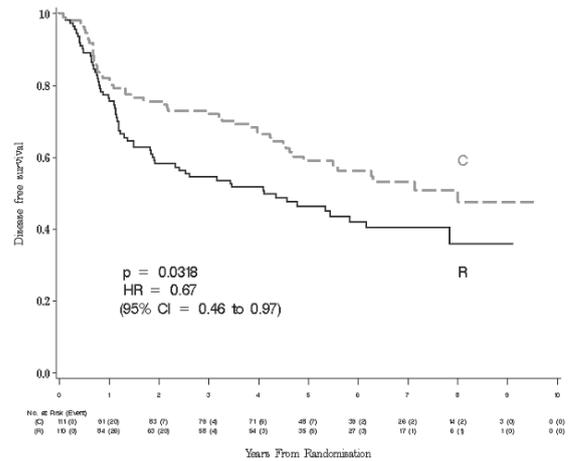


Fig. 1b. SQNP01: Five-year disease free survival.

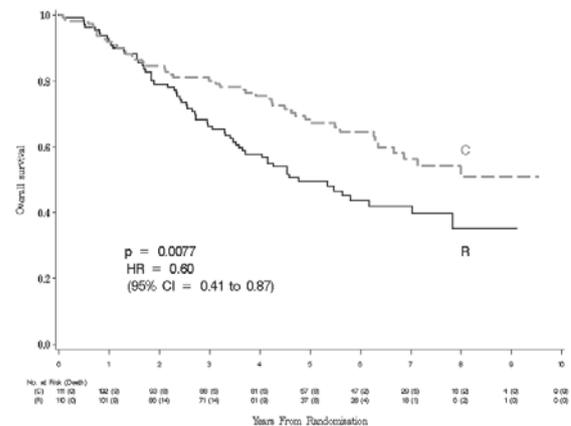


Fig. 1c. SQNP01: Five-year overall survival.

Table 1. Phase III Trials of Chemo-RT for Nasopharyngeal Carcinoma (Chemo-RT arm)

Author	Time point (y)	LRC (%)	PFS (%)	DFS (%)	DMF rate (%)	OS (%)
INT 00-99 ⁸	5		58	74		67
Wee (Singapore) ¹¹	3	88		72	85	80
	5			59	83	67
Lee (HK) ¹²	3	93	67		75	76
						(<i>P</i> = 0.97)
Ma (SYS) ¹⁷	2	97			86	87
Lin (Taiwan) ¹⁴	5	74	72	89	79	72
Chan (CUHK) ¹³	5		60		65	70
Zhang (PRC) ¹⁵	2	96		96	92	100
Kwong (HK) ¹⁶	5	78	68		84	81 NS
					CRT – sig	(<i>P</i> = 0.075)

Table 2. Phase III Trials According to Inclusion Criteria

Trial	Inclusion Criteria	Distribution of tumour burden?	Effect of chemo on dist mets?
Chan (CUHK) ¹³	N2, N3, >4 cm	High (35%)	NS
HK 99-01 ¹²	N2, N3	High (25%)	(76 vs 73) NS
INT 00-99 ⁸	Stage 3, 4	Ave	Sig
SQNP01 ¹¹	Stage 3, 4	Ave	(87 vs 70) Sig
Lin (Taiwan) ¹⁴	Stage 3, 4	Ave	15-20% (79 vs 70) Sig
Zhang (PRC) ¹⁵	Stage 3, 4	Ave	Sig
Kwong (QM) ¹⁶	[Stage 3, 4]	Ave	(85 vs 71) Sig
HK 99-0225	T3, T4 & N0, N1	Low 11%	(89 vs 81) NS

that the State of the Art for the Treatment of Locally Advanced NPC in 2008 – is the use of chemo-RT. However, there are still 2 issues remaining – firstly, the difference in outcome between the Hong Kong (HK99-01) and the Singapore (SQNP01) trials; and secondly the role of adjuvant chemotherapy in chemo-RT.

Difference in Outcomes Between the Hong Kong and Singapore Trials

Anne Lee and I presented the results of our respective trials at ASCO in 2004, and to the surprise of all present, our trials resulted in opposite outcomes – with the Hong Kong trial being negative, whereas the Singapore trial showed a survival benefit. Superficially both trials appeared similar – both were designed to confirm the validity of the 00-99 trial; both accrued only patients with the endemic form of NPC and the chemotherapy regimens used were similar.

Closer examination showed differences between the 2 trials: Firstly, the median follow-up period of the 2 trials

differed – it was 3.2 years for the Singapore trial and 2.3 years for HK99-01. When we went back and looked at the Data Monitoring Committee (DMC) Reports for SQNP01 – we realised that when the DMC met at a time point when the median follow-up was only 20 months – the difference between the 2 arms was not significantly different; and it only became statistically significant after a median follow-up period of 28 months. Similarly in another chemo-RT trial for NPC conducted by the Chinese University of Hong Kong (CUHK), the initial results published in 2002¹⁸ at a median follow-up of 2.7 years did not show a significant benefit with chemo-RT and it was only in 2005,¹³ after a median follow-up of 5.5 years that the results became significant. Thus, the possibility that the 2 trials differed in outcome could perhaps be attributed to the shorter period of the follow-up with HK99-01, and with longer follow-up, that trial might also become positive.

The second difference was the RT techniques and doses used. In SQNP01, which started earlier – all the patients were treated using conventional techniques. The dose was

also restricted to 70 Gy as there were concerns that any dose escalation with the use of concurrent chemotherapy may well result in unacceptable late radiation morbidity. For HK99-01 – about 50% of patients were treated using conformal techniques and the para-pharyngeal (PPS) boost (which would result in a dose escalation to 80-90 Gy) was routinely used. It was CUHK, which first published the results of the PPS boost,¹⁹ showing enhanced local control of patients with parapharyngeal extension of disease. In a subsequent study presented on behalf of the Hong Kong NPC Study Group,²⁰ Anne Lee showed that the 3 year OS of over 900 patients treated in the 2000 era was 74% - fairly similar to the results of the RT alone arm of HK99-01. Thus we could speculate that perhaps chemotherapy made up for lower RT doses!

The third difference was that the eligibility criteria for both trials differed. SQNP01 took in all patients with Stage III and IV disease, whereas HK99-01 included only patients with N2 or N3 disease, and specifically excluded patients with T3-4 and N0-1 disease who were accrued to the sister trial HK99-02 which examined the role of accelerated RT. Could it be that the Hong Kong trial accrued patients with an overall higher distant tumour burden compared with the Singapore cohort?

Lo²¹ from CUHK was the first to show the prognostic implication of pretreatment plasma EBV DNA concentration in NPC and which was found to correlate with disease stage. Subsequently Leung,²² also from CUHK, showed that pretreatment EBV DNA levels was predictive of post treatment distant failure. Lin from Taiwan in an article in the *New England Journal of Medicine*,²³ showed a very nice correlation between median concentrations of plasma EBV DNA and stage of disease. In a pre-clinical model,²⁴ the CUHK group showed a correlation between tumour mass and concentrations of plasma EBV DNA in nude mice inoculated with NPC tumour cells.

If we were to rearrange the table, which I had shown previously, but this time, arranging the trials according to inclusion criteria (Table 2) – a very striking picture appears. I will suggest that patients with N2 and N3 disease are most likely to have the highest distant tumour burden compared with patients which included all comers with Stage III and IV disease – and I will suggest that this second group will have an average tumour burden; and for patients with T3-4, N0-1 disease, they are most likely to have the lowest distant tumour burden. I think the distant failure outcomes in the chemo arm of the trials, does support this classification as shown in the middle column. The result – the 2 trials accruing only N2 and N3 patients - chemotherapy did not have any effect on distant disease; whereas all the trials accruing all comers with stage III and IV disease – and thus having an average distant tumour burden – all showed a

benefit of chemotherapy on distant disease, HK99-02²⁵ which was supposed to have a low distant tumour burden was negative – but I need to point out that this trial closed early and accrued less than 200 patients out of a planned sample size of over 400 – thus this trial is grossly underpowered. However the magnitude of difference is certainly more in keeping with the average tumour burden group.

Lin from Taiwan,²⁶ relooked at his trial and noted that chemo-RT did not appear to have an effect on those patients with high risks – i.e. patients with neck nodes greater than 6cm, with supraclavicular lymph nodes, with T4N2 disease and patients with multiple nodes with at least 1 node greater than 4 cm in size, On the other hand, chemo-RT resulted in improved survival in patients with “low risk” disease. Danial Chua²⁷ relooked at 2 trials – one from the Queen Mary Hospital and the other from Guangzhou and similarly found that induction chemotherapy improved distant control only in patients with early staged disease.

A more recent publication from the CUHK group²⁸ – showed a log linear correlation between pretreatment EBV DNA and tumour volume (both primary and nodes combined) as measured on MRI.

Since the majority of the males in this room have gone through National Service – I will attempt an analogy to make some sense to all this data – supposing, we had 1 battalion of cisplatin fighting 1 battalion of NPC – then I would suggest that the cisplatin had a fair chance of “victory”. However if it were 1 battalion of cisplatin fighting 4 brigades of NPC (as would be expected in cases where there is a high distant tumour burden) then the chances of “victory” would probably be slim!

Lin concludes that when patients with different prognostic factors are grouped within a single trial, the final results will depend on the proportion of patients from each staging group that is represented. Thus could it be that the difference in outcome between the Hong Kong and Singapore trials was because of a difference in distant tumour burden?

Role of Adjuvant Chemotherapy

The role of adjuvant chemotherapy was unfortunately not specifically addressed in the 8 trials that I had previously alluded to. Except for the Queen Mary trial, the others either did not have an adjuvant component, or if they did – was in combination with the concurrent chemotherapy that it was quite impossible to tease out its role separately.

Three trials have specifically addressed the issue of adjuvant chemotherapy. The Italian trial²⁹ looked at adjuvant VAC (vincristine, adriamycin and cyclophosphamide) – but these are older drugs with less individual efficacy. The TCOG trial³⁰ was also negative – but 78% of patients did not complete the adjuvant chemotherapy and the trial was

also closed early due to slow accruals. The Queen Mary trial³¹ – was well conducted. Unfortunately, it was conceived during an era when the “Goldie-Coleman Hypothesis” was still in vogue, and one questions today, whether by alternating the drugs – the dose intensity of individual drugs might have been compromised negating any efficacy that might have been present. A recent trial – a Phase II randomised trial of induction cisplatin and docetaxel was presented at ASCO in 2007 by the CUHK group,³² and the early results of this trial is promising.

2008 and Beyond

Thus we can conclude that concurrent chemo-RT works, but for the role of adjuvant chemotherapy – the jury is still out. The question now is “Where do we go from here?”

The issues that we currently face are: Can we further improve local control, and can we further improve distant control?

Control of Local Disease

Altered Fractionation RT

For local control, the MARCH meta-analysis³³ suggested a 7% absolute benefit for local control with altered fractionation RT, in squamous cell cancers of the head and neck (SCCHN). In NPC, the HK 99-02 trial²⁵ showed that the arm of 6 days a week RT with concurrent and adjuvant chemo-RT had the best 3 year actuarial local regional failure free survival.

IMRT

The second strategy to improve local control is the use of Intensity Modulated Radiotherapy (IMRT). Series from the US³⁴ as well as Hong Kong³⁵ have all shown high 90s percentage of local control. In 2002, we received an S\$3M Health Services Development Program (HSDP) grant from The Singapore Ministry of Health to develop IMRT for NPC. We recently looked at our own experience with the first 175 NPC patients treated with IMRT. The local control was 91% - similar to the series from The Chinese University Hong Kong (CUHK). We were a little disappointed with our results for T4 tumours – and we proceeded to perform an audit of our failures. To our relief, those that failed were more like “T5” to “T6” tumours with some tumours literally 1 mm from the brain stem or spinal cord, where it would be impossible to give curative doses without risking serious risks to the brainstem or spinal cord.

So, can we improve our local control – I think the resounding answer would be yes! But despite the excellent local control – the series from University of California, San Francisco (UCSF) where patients also received chemotherapy using the Al-Sarraf regimen still failed

distantly in about 34% of cases. So the issue is, can we also improve distant control?

Control of Distant Disease

Better control of distant disease would entail the need for better systemic therapy, and only drug dose escalation is likely to reduce the rate of distant metastases. It is unlikely that we would be able to escalate the dose of chemotherapy during the concurrent phase of chemo-RT any further because of toxicity. While adjuvant chemotherapy would have been ideal, the toxicity of chemo-RT is such that about 40% of patients are unable to tolerate and receive the full 3 courses of adjuvant chemotherapy after they had completed the concurrent chemo-RT phase. So can we improve treatment compliance by giving the adjuvant chemotherapy before rather than after the concurrent chemo-RT?

Induction Chemotherapy

Marshall Posner³⁶ has written extensively on this. In essence, although overall the MACH meta-analysis³⁷ showed no survival benefit with neo-adjuvant chemotherapy, a subset analysis³⁸ showed that if we only included trials where PF (cisplatin and 5FU) was used as the neo-adjuvant regimen (as opposed to other less effective regimens), that there was in fact a 5% favourable survival benefit. However, this positive result was only on meta-analysis and unfortunately, none of the individual trials were positive. In the Baujet meta-analysis³⁹ for NPC, neo-adjuvant chemotherapy did show a positive effect on distant control, although the effect on overall survival was again negative.

Induction versus Concurrent ChemoRT

At this point of time, it is interesting to bring out this paper from the University of Chicago group, which was published in the *Annals of Oncology* in 2004.⁴⁰ This essentially chronicled a decade of the Chicago experience with chemo-RT for SCCHN and is instructive. They performed a series of phase II trials for SCCHN, and during the early phase between 1989 till 1993, when neo-adjuvant chemotherapy was still in vogue, their trials also had an induction component. From 1993 till 1998, when neo-adjuvant chemotherapy fell out of favour, their trials also dropped the induction component. Their results for local and distant failure, is instructive. The 2 trials with the induction component had the lowest risk of distant failure.

We also looked at 2 Phase II trials for Stage IV NPC from Taipei, Taiwan – one from the National Taiwan University Hospital (NTUH)⁴¹ which used an induction regimen of MEPF1 – a 5 drug cocktail of MMC, Epirubicin, Platinum, 5FU and leucovorin and a second series from the Koo Foundation – Sun Yat Sen Cancer Center (SYS),⁴² where

their patients were treated with RT with 2 concurrent cycles of PF (cisplatin-5FU). The distant DFS free rate for Stage IV NPC patients for the NTUH series was 81% - better than the 67% from the SYS series.

BUT, for local control, the Chicago series – showed that those trials that utilised induction chemotherapy also did the worse; and similarly for our 2 Taiwanese NPC trials – the SYS trial did better than the NTUH trial for local control. Going back to the Baujat meta-analysis³⁹ for NPC, we see a similar pattern – concurrent chemotherapy doing better than induction chemotherapy for local control and conversely, induction doing better than concurrent for distant control.

Perhaps there is an explanation for this phenomena – Lester Peters⁴³ using radiobiological principles, attributes the poor local control with “neo-adjuvant regimens” to the prolonged overall treatment time taken to treat the primary tumour – resulting perhaps in the accelerated repopulation of tumours. Lucas Milas⁴⁴ from his Experimental Radiotherapy Laboratory at the MD Anderson Cancer Centre went 1 step further by showing in a mouse model, that accelerated repopulation did indeed occur after chemotherapy in mice; and the Institut Gustave Roussy Group under Bourhis et al,⁴⁵ showed it in patients with oropharyngeal tumours undergoing induction chemotherapy using a Tpot study.

Design for Future NPC Trials

It would thus appear that Induction chemotherapy followed by chemo-IMRT would be a worthwhile design to consider, although the issue of accelerated repopulation is still not addressed. Anne Lee’s group from The Pamela Youde Nethersole Eastern Hospital (PYNEH)⁴⁶ reported a series of Phase II trials using induction chemotherapy followed by concurrent platinum-accelerated (6 fractions/week) RT with promising results for Stage IV(A-B) NPC. So perhaps our new regimen should indeed be Induction Chemotherapy followed by chemo-accelerated IMRT!

The next issue is – How can we improve on the Al-Sarraf regimen, and give it as “neo-adjuvant” for better distant control? Trials of the addition of a taxane to PF (cisplatin-5FU) appear promising, and 4 trials⁴⁷⁻⁵⁰ comparing induction TPF vs. PF in SCCHN have already been reported and all 4 show statistically significant survival improvement with the triplet regimen. The Spanish Group lead by Ricardo Hitt⁵¹ – is currently investigating a very important question – a three-arm trial comparing induction with PF versus induction with the triplet TPF versus no-induction; and all followed by concurrent platinum-RT. At ASCO 2006, he presented preliminary data from that trial – and it looks as if at that point, the triplet induction arm appears to be leading. Thus, the use of triplet induction regimen appears

promising – at least in SCCHN.

So, is there any evidence that Induction concurrent chemo-RT works in NPC? Several small phase II trials suggest that it does. Danny Rischin⁵² reported the first trial, from the Peter MacCallum Cancer Institute. He used 3 cycles of a triplet combination of epirubicin, cisplatin and 5FU by continuous infusion, followed by cisplatin-RT. The 3-year PFS of 88% with 1 local recurrence for Stage IV NPC is certainly better than the UCSF⁵³ and MSKCC⁵⁴ series where the 3- and 2-year distant metastases free survival were 78% and 79% respectively. Other reports from CUHK,³² the Chicago group⁵⁵ and PYNEH⁴⁶ are also promising. Thus for NPC, the Phase II results are promising and we await Phase III trials to confirm.

Drug Regimen for Induction

The next issue is: Which drug combination should we use as induction? We looked back at our own experience with different regimens in the metastatic NPC setting. We started with PF⁵⁶ – and showed that we could achieve the same results as everyone else. Then when Carboplatin-Paclitaxel (CP) became popular in the USA, we did a Phase II trial of CP⁵⁷ for metastatic NPC – and essentially found that it gave similar results to PF, but CP patients had a better quality of life compared with PF. Gemcitabine then became available, and we conducted a phase II trial of this drug on metastatic NPC.⁵⁸ This trial was divided into 2 parts – for chemo-naïve patients, the overall response rate (ORR) to gemcitabine was 28%; but what made us sit up, was the fact that patients who failed prior CP had a 48% ORR. Considering that most chemotherapy give only 10% to 20% ORR in the metastatic setting, this result suggested to us that perhaps gemcitabine had an effect on a clone of cells resistant to CP. It thus made sense for us to add gemcitabine to CP – and our next trial tested this new triplet combination. The excellent response of gemcitabine as second line therapy was recently confirmed in another trial from the Guangzhou Sun Yet Sen group⁵⁹ – that reported a 44% ORR.

Our trial of the triplet combination of Gemcitabine, Carboplatin and Paclitaxel (GCP)⁶⁰ yielded an ORR of 85% and a median survival of 18 months. This compares very favourably with our prior experience with doublets that produced median survivals of about 12 months. In a subsequent trial, we added maintenance 5FU after GCP⁶¹ (based on the promising results from Hong et al⁶² from NTUH – using maintenance 5FU after MEPFL), and obtained a median survival of 22 months for this cohort. In terms of median survivals, the triplet combination of GCP is certainly promising. As much as we would have loved to perform a Phase III randomised trial of this triplet against a standard doublet, it would be unrealistic – given the smaller number of patients with metastatic disease available

nowadays.

We thus took a step of faith, and decided to test this combination in the adjuvant setting instead. So we launched a randomised phase II trial comparing cisplatin-IMRT with or without induction GCP. In 2007, we received a Singapore Ministry of Health, National Medical Research Council (NMRC) grant for this trial. Our intention is for the randomised phase II trial to serve as a pilot, and we will convene a Data and Safety Monitoring Board (DSMB) once we complete accrual to this trial; with a view of continuing this trial into a phase III setting, and the question we hope to answer is whether such a strategy can improve the 5 year overall survival rate to 80% from the current 70% with chemo-RT.

The Future

As we peek into the crystal ball, and try to predict the future, our bet is on immunotherapy – specifically adoptive T-cell therapy. For the non-immunologist, my friend Dr Toh Han Chong uses the Hong Kong movie “Infernal Affairs” to explain the mechanics of T-cell therapy. Infernal Affairs is the story of a policeman who has worked undercover with the triads for such a long time that, he has forgotten whether he is a cop or a triad member! The aim is thus to bring him out of the triads, and back to the police academy to retrain him to think like a policeman. Similarly, in NPC, the T-cells – which should have acted as the body’s policemen – seem not to be able to recognize the NPC cells as “enemy”; so the idea is to take the T-cells out of the body – expose them to the EB virus, retrain them, and then reinfuse them into the patient, so that the T-cells can now recognize the NPC cells as foreign and destroy them.

Dr Toh is the Principal Investigator of a non-myeloablative allogeneic blood stem cell transplant (NMBSCT) trial, and reported at ASCO 2006⁶³ an impressive ORR of about 40% for this treatment in patients with chemo-refractory metastatic NPC. Two groups have reported very promising results with adoptive immunotherapy,^{64,65} with ORR of 60% to 70%. With such impressive preliminary results, one wonders if this a reprise of the gemcitabine story all over again? There were difficulties with the NMBSCT trial, as it required donors from siblings. Our group will thus test adoptive T-cell therapy in the first line metastatic setting, and should this result be promising, then we foresee that a possible replacement trial after the induction chemotherapy – concurrent chemotherapy trial (assuming this becomes the new standard of care) would be a Phase III trial of the induction chemotherapy with concurrent chemo-IMRT with or without consolidation with adoptive T-cell therapy. And if we are able to achieve an 80% cure rate with the induction regimen; can we achieve a 90% cure rate by consolidating with adoptive T-cell therapy?

Conclusion

The Cancer Incidence Trend⁶⁶ for NPC remains relatively flat for the last 30 years, and has only started to take a dip in the last 5 years. However the Cancer Mortality Trends for NPC appears to be slowly declining. I had previously shown the results of the 1992-94 cohort – which had an overall 5-year survival of 57%. We looked at our 2000-04 cohort – and this group’s actuarial 5-year overall survival is currently 68% – and we would like to think that our NPC workgroup had in some measure contributed a little to this improvement.

Finally, I would like to acknowledge the contribution of my colleagues at the Department of Radiation Oncology; the Head, Neck and Lung Team from the Department of Medical Oncology, NCC – and especially Dr Tan Eng Huat – whom I have worked with closely for the last decade; the co-coordinators and statisticians at my Division of Clinical Trials and Epidemiological Sciences and last but not least Dr Vijay Kumar Sethi – my boss, my teacher and my mentor. He was the one that egged us on and said “If we cannot be good in everything, let us try to be good in at least one thing”. Our efforts in NPC would not have succeeded if not for his foresight and encouragement. And with that ladies and gentlemen, I thank you.

REFERENCES

1. Khoo FY, Chia KB, Nalpon J. A new technique of contrast examination of the nasopharynx with cinefluorography and roentgenography. *Am J Roentgenol Radium Ther Nucl Med* 1967;99:238-48.
2. Chong VFH, Tsao SY. *Nasopharyngeal carcinoma*. Armour Publishing, Singapore, 1997.
3. Chua MLK, Gao F, Khoo J, Ong SC, Ng D, Wee J, et al. Comparison of 4 modalities for distant metastases staging in endemic nasopharyngeal carcinoma. *Proceedings of the 49th ASTRO*, Los Angeles, USA, 2007.
4. Heng DM, Wee J, Fong KW, Lian LG, Sethi VK, Chua ET, et al. Prognostic factors in 677 patients with non-disseminated nasopharyngeal carcinoma in Singapore. *Cancer* 1999;86:1912-20.
5. Lee AW, Poon YF, Foo W, Law SC, Cheung FK, Chan DK, et al. Retrospective analysis of 5037 patients with nasopharyngeal carcinoma treated during 1976-1985: overall survival and patterns of failure. *Int J Radiat Oncol Biol Phys* 1992;23:261-70.
6. O’Sullivan B, Strong E, Ho J, Teo P, Lee A, Chua EJ, et al. The AJCC/UICC Nasopharyngeal Carcinoma Staging Classification for the 5th Edition of The TNM. *Proceedings 4th International Conference on Head and Neck Cancer*, Toronto, Canada 1996.
7. Tham WK, Yap SP, Tuan J, Hee SW, Wee J. Retropharyngeal nodal metastasis is related to a higher rate of distant metastasis in patients with nasopharyngeal cancer – results from a single centre retrospective study. *Proceedings ECCO-14*, Barcelona, Spain 2007. *Eur J Cancer* 2007;Suppl 5:331.
8. Al-Sarraf M, LeBlanc M, Giri PG, Fu KK, Cooper J, Vuong T, et al. Chemoradiotherapy versus radiotherapy in patients with advanced nasopharyngeal cancer: phase III randomized Intergroup study 0099. *J Clin Oncol* 1998;16:1310-7.
9. Chan AT, Teo PM, Johnson PJ. Controversies in the management of

- locoregionally advanced nasopharyngeal carcinoma. *Curr Opin Oncol* 1998;10:219-25.
10. Tan EH, Chua ET, Wee J, Tan T, Fong KW, Ang PT, et al. Concurrent chemoradiotherapy followed by adjuvant chemotherapy in Asian patients with nasopharyngeal cancer: toxicities and preliminary results. *Int J Radiat Oncol Biol Phys* 1999;45:597-601.
 11. Wee J, Tan EH, Tai BC, Wong HB, Leong SS, Tan T, et al. Randomized trial of radiotherapy versus concurrent chemo-radiotherapy followed by adjuvant chemotherapy in patients with AJCC/UICC (1997) Stage III and IV nasopharyngeal cancer of the endemic variety. *J Clin Oncol* 2005;23:6730-8.
 12. Lee AW, Lau WH, Tung SY, Chua DT, Chappell R, Xu L, et al; Hong Kong Nasopharyngeal Cancer Study Group. Preliminary results of a randomized study on therapeutic gain by concurrent chemotherapy for regionally-advanced nasopharyngeal carcinoma: NPC-9901 Trial by the Hong Kong Nasopharyngeal Cancer Study Group. *J Clin Oncol* 2005;23:6966-75.
 13. Chan AT, Leung SF, Ngan RK, Teo PM, Lau WH, Kwan WH, et al. Overall survival after concurrent cisplatin-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma. *J Natl Cancer Inst* 2005;97:536-9.
 14. Lin JC, Jan JS, Hsu CY, Liang WM, Jiang RS, Wang WY. Phase III study of concurrent chemoradiotherapy versus radiotherapy alone for advanced nasopharyngeal carcinoma: positive effect on overall and progression-free survival. *J Clin Oncol* 2003;21:631-7.
 15. Zhang L, Zhao C, Peng PJ, Lu LX, Huang PY, Han F, et al. Phase III study comparing standard radiotherapy with or without weekly oxaliplatin in treatment of locoregionally advanced nasopharyngeal carcinoma: preliminary results. *J Clin Oncol* 2005;23:8461-8.
 16. Kwong DL, Sham JS, Au GK, Chua DT, Kwong PW, Cheng AC, et al. Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. *J Clin Oncol* 2004;22:2643-53.
 17. Ma J, Chen Y, Liu MZ, Liang SB, Zong JF, Guo Y, et al. Preliminary results of a prospective randomized trial comparing concurrent chemoradiotherapy plus adjuvant chemotherapy versus radiotherapy alone in patients with locoregionally advanced Nasopharyngeal Carcinoma in endemic regions. *Proceedings East West Symposium on Nasopharyngeal Carcinoma*. Sunshine Coast, Australia, 2007.
 18. Chan AT, Teo PM, Ngan RK, Leung TW, Lau WH, Zee B, et al. Concurrent chemotherapy-radiotherapy compared with radiotherapy alone in locoregionally advanced nasopharyngeal carcinoma: progression-free survival analysis of a phase III randomized trial. *J Clin Oncol* 2002;20:2038-44.
 19. Teo P, Tsao SY, Shiu W, Leung WT, Tsang V, Yu P, et al. A clinical study of 407 cases of nasopharyngeal carcinoma in Hong Kong. *Int J Radiat Oncol Biol Phys* 1989;17:515-30.
 20. Lee AW, Sze WM, Au JS, Leung SF, Leung TW, Chua DT, et al. Treatment results for nasopharyngeal carcinoma in the modern era: the Hong Kong experience. *Int J Radiat Oncol Biol Phys* 15;61:1107-16.
 21. Lo YM. Prognostic implication of pretreatment plasma/serum concentration of Epstein-Barr virus DNA in nasopharyngeal carcinoma. *Biomed Pharmacother* 2001;55:362-5.
 22. Leung SF, Chan AT, Zee B, Ma B, Chan LY, Johnson PJ, et al. Pretherapy quantitative measurement of circulating Epstein-Barr virus DNA is predictive of posttherapy distant failure in patients with early-stage nasopharyngeal carcinoma of undifferentiated type. *Cancer* 2003;98:288-91.
 23. Lin JC, Wang WY, Chen KY, Wei YH, Liang WM, Jan JS, et al. Quantification of plasma Epstein-Barr virus DNA in patients with advanced nasopharyngeal carcinoma. *N Engl J Med* 2004;350:2461-70.
 24. Chan KC, Chan AT, Leung SF, Pang JC, Wang AY, Tong JH, et al. Investigation into the origin and tumoral mass correlation of plasma Epstein-Barr virus DNA in nasopharyngeal carcinoma. *Clin Chem* 2005;51:2192-5.
 25. Lee AW, Tung SY, Chan AT, Chappell R, Fu YT, Lu TX, et al. Preliminary results of a randomized study (NPC-9902 Trial) on therapeutic gain by concurrent chemotherapy and/or accelerated fractionation for locally advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2006;66:142-51.
 26. Lin JC, Liang WM, Jan JS, Jiang RS, Lin AC. Another way to estimate outcome of advanced nasopharyngeal carcinoma – is concurrent chemoradiotherapy adequate? *Int J Radiat Oncol Biol Phys* 2004;60:156-64.
 27. Chua DT, Ma J, Sham JS, Mai HQ, Choy DT, Hong MH, et al. Improvement of survival after addition of induction chemotherapy to radiotherapy in patients with early-stage nasopharyngeal carcinoma: Subgroup analysis of two Phase III trials. *Int J Radiat Oncol Biol Phys* 2006;65:1300-6.
 28. Ma BB, King A, Lo YM, Yau YY, Zee B, Hui EP, et al. Relationship between pretreatment level of plasma Epstein-Barr virus DNA, tumor burden, and metabolic activity in advanced nasopharyngeal carcinoma. *Int J Radiat Oncol Biol Phys* 2006;66:714-20.
 29. Rossi A, Molinari R, Boracchi P, Del Vecchio M, Marubini E, Nava M, et al. Adjuvant chemotherapy with vincristine, cyclophosphamide, and doxorubicin after radiotherapy in local-regional nasopharyngeal cancer: results of a 4-year multicenter randomized study. *J Clin Oncol* 1988;6:1401-10.
 30. Chi KH, Chang YC, Guo WY, Leung MJ, Shiau CY, Chen SY, et al. A phase III study of adjuvant chemotherapy in advanced nasopharyngeal carcinoma patients. *Int J Radiat Oncol Biol Phys* 2002;52:1238-44.
 31. Kwong DL, Sham JS, Au GK, Chua DT, Kwong PW, Cheng AC, et al. Concurrent and adjuvant chemotherapy for nasopharyngeal carcinoma: a factorial study. *J Clin Oncol* 2004;22:2643-53.
 32. Hui EP, Ma BB, Leung SF, King A, Mo F, Kam MK, et al. Efficacy of neoadjuvant docetaxel and cisplatin followed by concurrent cisplatin-radiotherapy in locally advanced nasopharyngeal carcinoma (NPC): A randomized phase II study. *ASCO Annual Meeting Proceedings Part I*. *J Clin Oncol* 2007;25(June 20 Suppl):6037.
 33. Bourhis J, Overgaard J, Audry H, Ang KK, Saunders M, Bernier J, et al; Meta-Analysis of Radiotherapy in Carcinomas of Head and neck (MARCH) Collaborative Group. Hyperfractionated or accelerated radiotherapy in head and neck cancer: a meta-analysis. *Lancet* 2006;368:843-54.
 34. Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys* 2002;53:12-22.
 35. Kam MK, Teo PM, Chau RM, Cheung KY, Choi PH, Kwan WH, et al. Treatment of nasopharyngeal carcinoma with intensity-modulated radiotherapy: the Hong Kong experience. *Int J Radiat Oncol Biol Phys* 2004;60:1440-50.
 36. Posner MR. Paradigm shift in the treatment of head and neck cancer: the role of neoadjuvant chemotherapy. *Oncologist* 2005;10 Suppl 3:11-9.
 37. Pignon JP, le Maître A, Bourhis J; MACH-NC Collaborative Group. Meta-Analyses of Chemotherapy in Head and Neck Cancer (MACH-NC): an update. *Int J Radiat Oncol Biol Phys* 2007;69(2 Suppl):S112-4.
 38. Monnerat C, Faivre S, Temam S, Bourhis J, Raymond E. End points for new agents in induction chemotherapy for locally advanced head and neck cancers. *Ann Oncol* 2002;13:995-1006.
 39. Baujat B, Audry H, Bourhis J, Chan AT, Onat H, Chua DT, et al; MAC-NPC Collaborative Group. Chemotherapy in locally advanced nasopharyngeal carcinoma: an individual patient data meta-analysis of eight randomized trials and 1753 patients. *Int J Radiat Oncol Biol Phys* 2006;64:47-56.
 40. Brockstein B, Haraf DJ, Rademaker AW, Kies MS, Stenson KM, Rosen F, et al. Patterns of failure, prognostic factors and survival in locoregionally advanced head and neck cancer treated with concomitant chemoradiotherapy: a 9-year, 337-patient, multi-institutional experience. *Ann Oncol* 2004;15:1179-86.

41. Hong RL, Ting LL, Ko JY, Hsu MM, Sheen TS, Lou PJ, et al. Induction chemotherapy with mitomycin, epirubicin, cisplatin, fluorouracil, and leucovorin followed by radiotherapy in the treatment of locoregionally advanced nasopharyngeal carcinoma. *J Clin Oncol* 2001;19:4305-13.
42. Cheng SH, Liu TW, Jian JJ, Tsai SY, Hao SP, Huang CH, et al. Concomitant chemotherapy and radiotherapy for locally advanced nasopharyngeal carcinoma. *Cancer J Sci Am* 1997;3:100-6.
43. Peters LJ, Withers HR. Applying radiobiological principles to combined modality treatment of head and neck cancer – the time factor. *Int J Radiat Oncol Biol Phys* 1997;39:831-6.
44. Milas L, Nakayama T, Hunter N, Jones S, Lin TM, Yamada S, et al. Dynamics of tumor cell clonogen repopulation in a murine sarcoma treated with cyclophosphamide. *Radiother Oncol* 1994;30:247-53.
45. Bourhis J, Wilson G, Wibault P, Janot F, Bosq J, Armand JP, et al. Rapid tumor cell proliferation after induction chemotherapy in oropharyngeal cancer. *Laryngoscope*. 1994;104:468-72.
46. Yau TK, Lee AW, Wong DH, Pang ES, Ng WT, Yeung RM, et al. Treatment of stage IV (A-B) nasopharyngeal carcinoma by induction-concurrent chemoradiotherapy and accelerated fractionation: impact of chemotherapy schemes. *Int J Radiat Oncol Biol Phys* 2006;66:1004-10.
47. Hitt R, López-Pousa A, Martínez-Trufero J, Escrig V, Carles J, Rizo A, et al. Phase III study comparing cisplatin plus fluorouracil to paclitaxel, cisplatin, and fluorouracil induction chemotherapy followed by chemoradiotherapy in locally advanced head and neck cancer. *J Clin Oncol* 2005;23:8636-45. Erratum in: *J Clin Oncol* 2006;24:1015.
48. Vermorcken JB, Remenar E, van Herpen C, Gorlia T, Mesia R, Degardin M, et al; EORTC 24971/TAX 323 Study Group. Cisplatin, fluorouracil, and docetaxel in unresectable head and neck cancer. *N Engl J Med* 2007;357:1695-704.
49. Posner MR, Hershock DM, Blajman CR, Mickiewicz E, Winquist E, Gorbounova V, et al; TAX 324 Study Group. Cisplatin and fluorouracil alone or with docetaxel in head and neck cancer. *N Engl J Med* 2007;357:1705-15.
50. Calais G, Pointreau Y, Alfonsi M, Sire C, Tuchais C, Tortochaux J, et al. Randomized phase III trial comparing induction chemotherapy using cisplatin (P) fluorouracil (F) with or without docetaxel (T) for organ preservation in hypopharynx and larynx cancer. Preliminary results of GORTEC 2000-01. ASCO Annual Meeting Proceedings Part I. *J Clin Oncol* 2006;24(18S):5506.
51. Hitt R, Grau J, Lopez-Pousa A, Berrocal A, García-Giron C, Belon J, et al. Randomized phase II/III clinical trial of induction chemotherapy (ICT) with either cisplatin/5-fluorouracil (PF) or docetaxel/cisplatin/5-fluorouracil (TPF) followed by chemoradiotherapy (CRT) vs. crt alone for patients (pts) with unresectable locally advanced head and neck cancer (LAHNC). ASCO Annual Meeting Proceedings Part I. *J Clin Oncol* 2006;24(18S):5515.
52. Rischin D, Corry J, Smith J, Stewart J, Hughes P, Peters L. Excellent disease control and survival in patients with advanced nasopharyngeal cancer treated with chemoradiation. *J Clin Oncol* 2002;20:1845-52.
53. Lee N, Xia P, Quivey JM, Sultanem K, Poon I, Akazawa C, et al. Intensity-modulated radiotherapy in the treatment of nasopharyngeal carcinoma: an update of the UCSF experience. *Int J Radiat Oncol Biol Phys* 2002;53:12-22.
54. Wolden SL, Chen WC, Pfister DG, Kraus DH, Berry SL, Zelefsky MJ. Intensity-modulated radiation therapy (IMRT) for nasopharynx cancer: update of the Memorial Sloan-Kettering experience. *Int J Radiat Oncol Biol Phys* 2006;64:57-62.
55. Oh JL, Vokes EE, Kies MS, Mittal BB, Witt ME, Weichselbaum RR, et al. Induction chemotherapy followed by concomitant chemoradiotherapy in the treatment of locoregionally advanced nasopharyngeal cancer. *Ann Oncol* 2003;14:564-9.
56. Au E, Ang PT. A phase II trial of 5-fluorouracil and cisplatin in recurrent or metastatic nasopharyngeal carcinoma. *Ann Oncol* 1994;5:87-9.
57. Tan EH, Khoo KS, Wee J, Fong KW, Lee KS, Lee KM, et al. Phase II trial of a paclitaxel and carboplatin combination in Asian patients with metastatic nasopharyngeal carcinoma. *Ann Oncol* 1999;10:235-7.
58. Foo KF, Tan EH, Leong SS, Wee JT, Tan T, Fong KW, et al. Gemcitabine in metastatic nasopharyngeal carcinoma of the undifferentiated type. *Ann Oncol* 2002;13:150-6.
59. Zhang L, Zhang Y, Huang PY, Xu F, Peng PJ, Guan ZZ. Phase II clinical study of gemcitabine in the treatment of patients with advanced nasopharyngeal carcinoma after the failure of platinum-based chemotherapy. *Cancer Chemother Pharmacol* 2008;61:33-8.
60. Leong SS, Wee J, Tay MH, Toh CK, Tan SB, Thng CH, et al. Paclitaxel, carboplatin, and gemcitabine in metastatic nasopharyngeal carcinoma: a Phase II trial using a triplet combination. *Cancer* 2005;103:569-75.
61. Leong SS, Wee J, Rajan S, Toh CK, Lim WT, Hee SW, et al. Triplet combination of gemcitabine, paclitaxel, and carboplatin followed by maintenance 5-fluorouracil and folinic acid in patients with metastatic nasopharyngeal carcinoma. *Cancer* 2008 Jul 9 [Epub ahead of print].
62. Hong RL, Sheen TS, Ko JY, Hsu MM, Wang CC, Ting LL. Induction with mitomycin C, doxorubicin, cisplatin and maintenance with weekly 5-fluorouracil, leucovorin for treatment of metastatic nasopharyngeal carcinoma: a phase II study. *Br J Cancer* 1999;80:1962-7.
63. Toh HC, Tan EH, Thng CH, Yap SP, Lee KM, Phoon YP, et al. Non-myeloablative allogeneic blood stem cell transplantation (NMBST) ± donor lymphocyte infusion (DLI) for chemorefractory advanced nasopharyngeal carcinoma (NPC). ASCO Annual Meeting Proceedings. *J Clin Oncol* 2006;24(18S):2549.
64. Gottschalk S, Bollard C, Straathoff K, Shaffer D, Torrano V, Cooper-Havlik D, et al. Adoptive Immunotherapy for Nasopharyngeal Carcinoma. Proceedings East-West Symposium in Nasopharyngeal Carcinoma. Brisbane, Australia, 2007.
65. Comoli P, Pedrazzoli P, Maccario R, Basso S, Carminati O, Labirio M, et al. Cell therapy of stage IV nasopharyngeal carcinoma with autologous Epstein-Barr virus-targeted cytotoxic T lymphocytes. *J Clin Oncol* 2005;23:8942-9.
66. Seow A, Koh WP, Chia KS, Shi LM, Lee HP, Shanmugaratnam K. Trends in Cancer Incidence in Singapore 1968-2002. Singapore: Singapore Cancer Registry, 2004. Report No 6.