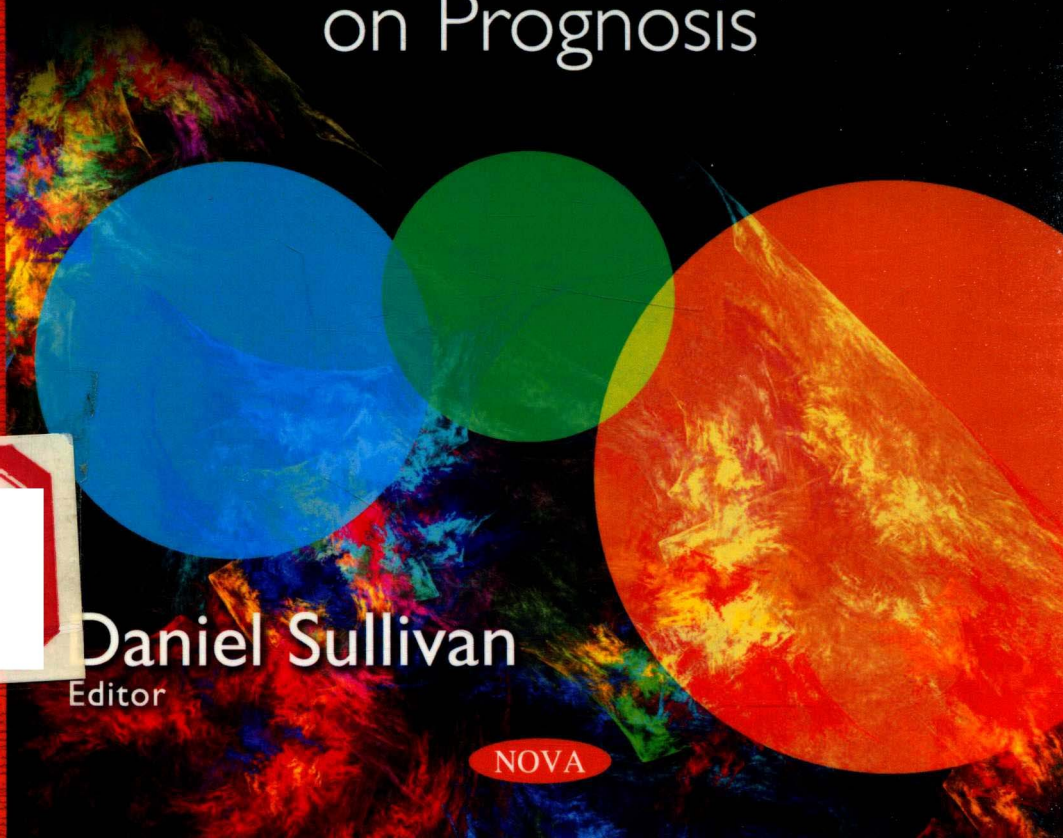
Cancer Etiology, Diagnosis and Treatments

Chemoradiotherapy

Concurrent Uses, Efficacy and Impact on Prognosis



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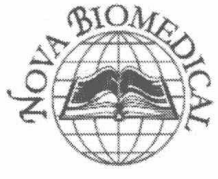
DANIEL SULLIVAN
EDITOR



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PREFACE

Chemoradiotherapy is the use of both chemotherapy and radiotherapy for the treatment of cancer. This book discusses its concurrent uses, efficacy in the medical field, and the impact it has on the prognosis of cancers.

Chapter 1 – The current treatment paradigm in locally advanced nasopharyngeal cancer (NPC) is concurrent chemoradiotherapy with advanced radiotherapy techniques. Since the landmark Intergroup 0099 trial, the addition of chemotherapy to radiotherapy has an established role to improve survival outcomes compared with radiotherapy alone. More randomized studies have confirmed the survival benefit of following the Intergroup regimen of concurrent chemoradiotherapy plus adjuvant chemotherapy. However, the optimal sequence of chemotherapy and the additional value of induction versus adjuvant chemotherapy to the concurrent scheme remains to be controversial. Many studies have attempted to answer the question, and the recent update of MAC NPC meta-analysis has explored the distinct roles of concomitant and adjuvant chemotherapy. The extension of the concurrent scheme to stage II is still a subject of debate. Pattern of failure analyses may be able to shed light on identification of prognostic factors and risk groups that can guide treatment decisions. Related to its Epstein-Barr virus (EBV) association in the pathogenesis of NPC, circulating EBV-DNA load has been demonstrated to have prognostic significance for patients treated with concurrent chemoradiotherapy. Further studies are warranted to investigate the role of EBV DNA asa pre-treatment or post-treatment indicator of treatment outcome, and potential role of other biomarkers for prognostication.

Chapter 2 – Although the majority of patients present with non-muscle-invasive bladder cancer, 20–40% of these patients eventually develop muscle-invasive lesions. The survival rate is poor for bladder cancer, with only about

45% of patients surviving for 5 years, regardless of the type of treatment. Cisplatin-based systemic chemotherapy, such as a combination of methotrexate, vinblastine, doxorubicin, and cisplatin or a combination of gemcitabine and cisplatin, is the recommended standard treatment for inoperably advanced or metastatic bladder cancer. Although multimodal treatment has become the standard of care for other kinds of malignancy, in patients with muscle-invasive bladder cancer chemoradiotherapy is performed in an effort to preserve the bladder. Chemoradiotherapy for the treatment of advanced bladder cancer remains questionable, however, as it is unclear whether this will eradicate local disease, eliminate potential micrometastases, and maintain the best quality of life possible without compromising survival. Concurrent chemoradiotherapy has an advantage over external beam radiation therapy alone, but only a few randomized trials have compared these two approaches to the treatment of muscle-invasive cancer. Even in the absence of more effective systemic therapy, improving bladder preservation treatments could provide patients with a choice of treatment and improve quality of life. We previously reported on the efficacy of chemoradiotherapy, and here we review the association of this modality with muscle-invasive bladder cancer.

Chapter 3 – The management options for patients with locally-advanced rectal cancer are evolving. When Heald popularised the concept of total mesorectal excision (TME) 30 years ago, the prognostic benefit of oncological therapy was largely unknown. The standardisation of surgery was the single-most important change that led to the current low local recurrence rates. The modern tools for treating rectal cancer now include short or long-course pre-operative radiotherapy, a variety of surgical techniques able to address a wide range of tumours from early lesions to the locally advanced, and combination adjuvant chemotherapy. In many cases there is a simple binary choice - for example, radiotherapy will be given for those tumours at high risk of a local recurrence as demonstrated by objective staging criteria whereas not for presumed early lesions. Similarly, surgical technique will be decided on the depth of tumour invasion and if it does not breach the muscularis then a local procedure may be appropriate as opposed to radical resection. These decisions are largely informed by using high-resolution MRI which is now seen as mandatory for accurate local staging. But with such an array of management options, why do we remain relatively prescriptive in our approach to rectal cancer?

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Chapter 1

EVIDENCED-BASED MANAGEMENT OF NASOPHARYNGEAL CANCERS IN THE MODERN ERA

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ABSTRACT

The current treatment paradigm in locally advanced nasopharyngeal cancer (NPC) is concurrent chemoradiotherapy with advanced radiotherapy techniques. Since the landmark Intergroup 0099 trial, the addition of chemotherapy to radiotherapy has an established role to improve survival outcomes compared with radiotherapy alone. More randomized studies have confirmed the survival benefit of following the Intergroup regimen of concurrent chemoradiotherapy plus adjuvant chemotherapy. However, the optimal sequence of chemotherapy and the additional value of induction versus adjuvant chemotherapy to the concurrent scheme remains to be controversial. Many studies have attempted to answer the question, and the recent update of MAC NPC meta-analysis has explored the distinct roles of concomitant and adjuvant

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chemotherapy. The extension of the concurrent scheme to stage II is still a subject of debate. Pattern of failure analyses may be able to shed light on identification of prognostic factors and risk groups that can guide treatment decisions. Related to its Epstein-Barr virus (EBV) association in the pathogenesis of NPC, circulating EBV-DNA load has been demonstrated to have prognostic significance for patients treated with concurrent chemoradiotherapy. Further studies are warranted to investigate the role of EBV DNA asa pre-treatment or post-treatment indicator of treatment outcome, and potential role of other biomarkers for prognostication.

Keywords: nasopharyngeal cancer, chemoradiation, MAC NPC meta-analysis

INTRODUCTION

Report from GLOBOCAN by the International Agency for Research on Cancer (IARC) showed that the total number of new cases of nasopharyngeal cancer (NPC) in the world was 86691 and the total number of deaths was 50831 in the year 2012 [1].. This cancer has a distinctive racial and geographical distribution; over 80% of new cases occurred in Asia and 9% in Africa. Genetic predisposition, dietary habits and previous exposure to Epstein-Barr virus (EBV) are other important risk factors [2–5].

Radiotherapy (RT) is the primary treatment modality, but with randomized trials and meta-analyses confirming the therapeutic benefit by adding chemotherapy, concurrent ± sequential chemoradiotherapy has become the standard recommendation for patients with locoregionally advanced disease. There is little controversy that sequential chemotherapy alone is inadequate for achieving survival benefit, but questions remain whether addition of sequential chemotherapy could further improve the results of concurrent chemoradiotherapy (C-CRT); and if yes, what is the most potent sequence (induction-concurrent versus concurrent-adjuvant). Most of the previous trials are based on patients irradiated with 2-dimensional technique; with rapid advances of RT technology in the past 2 decades, re-evaluation of the magnitude of benefit by chemotherapy with modern radiotherapy is needed. In addition, the pressing question is whether we can use emerging predictive and prognostic markers to accurately identify high-risk patients for chemoradiotherapy [6-24]. This review provides a comprehensive summary on the current data about concurrent ± sequential chemoradiotherapy outcome of

patients treated with modern radiation techniques, and novel research directions for the management of this unique malignancy.

CONCURRENT WITH AND WITHOUT ADJUVANT CHEMOTHERAPY

The Intergroup 0099 (INT-0099) trial is the first phase III study that achieved significant survival benefit [25]. The regimen is composed of cisplatin 100mg/m^2 on day 1, 22 and 43 of radiotherapy followed by three additional cycles of adjuvant chemotherapy using cisplatin 80mg/m^2 on day 1 and 5-fluorouracil 1000mg/m^2 from day 1 to 4 at 4 weeks after completion of concurrent chemoradiotherapy. Of 147 patients eligible for primary analysis, the concurrent-adjuvant CRT arm achieved significantly better outcome than the RT alone arm both in terms of 3-year progression-free survival (PFS: 69% vs. 24%, $p < 0.001$), and overall survival (OS: 78% vs. 47%). Updated results at five years confirmed the superiority of the chemoradiotherapy arm (5-year OS 67% vs. 37%).

When the result of this study was first published in 1998, there were serious concerns about the magnitude of benefit and the general applicability because the OS rate in the RT alone arm was substantially lower than results commonly achievable by major centers, the compliance rate in the adjuvant phase was poor, the impact on late toxicity was unknown, and the proportion of keratinizing histology was much higher than the usual pattern in endemic regions. Hence, this stimulated subsequent confirmatory trials from endemic regions.

The first patient-data meta-analysis (MAC-NPC_1), based on 1753 patients from eight trials, was published in 2006, The conclusion was that addition of chemotherapy led to a small, but significant, benefit (6% improvement, from 56% to 62% in OS at 5 years, hazard ratio [HR] 0.82, 95% confidence interval [CI] 0.71 – 0.94, $p = 0.006$) [26]. The concurrent trials showed a better treatment effect than induction or adjuvant chemotherapy (HR 0.60, 95% CI 0.48 – 0.76 versus HR 0.99, 95% CI 0.80 – 1.21 and HR 0.97, 95% CI 0.69 – 1.38 respectively). This further established the role of concurrent CRT as the standard treatment for locoregionally advanced NPC. However, it should be noted that the concurrent trials included in this meta-analysis were the Intergroup 0099 trial using concurrent-adjuvant CRT, the trial by Chan et al. (using concurrent chemotherapy with weekly cisplatin) and

that by Kwong et al. (using concurrent chemotherapy with Uracil-Tegafur ± adjuvant chemotherapy with Cisplatin-Fluorouracil alternating with Vincristine-Bleomycin-Methotrexate) [27, 28]. There were no separate analyses on concurrent-adjuvant trials versus concurrent-alone trials.

In the following years, confirmatory trials from Singapore (by Wee et al.), from Hong Kong (NPC-9901 and NPC-9902 trials by Lee et al.) and mainland China (by Chen et al.), all using concurrent cisplatin and adjuvant cisplatin-fluorouracil, consistently confirmed the efficacy of concurrent-adjuvant CRT for event-free survival [29-32]. The NPC-9901 trial, which focused on patients with N2-3 disease, was the only trial that raised the caution that this regimen may not be adequate for distant control of regionally advanced patients; interestingly, although the impact on OS was initially negative, this became significant with long-term follow-up [30, 33]. In addition, a combined analysis of patients from NPC-9901 and NPC-9902 treated by conventional-fractionated RT revealed that concurrent chemotherapy had significant impact on locoregional control, whereas adjuvant chemotherapy (particularly the dose of fluorouracil) was important for distant control [34]. As the benefit in patients who had received 2 concurrent cycles was similar to those who had 3 cycles, 200mg/m^2 of concurrent cisplatin may be adequate for locoregional control. Thus far, there have been six randomized trials using concurrent-alone CRT, various chemotherapy regimen was used, and the results were heterogeneous. Only the trial by Chen et al. using cisplatin for Stage II patients and that by Wu et al. using oxaliplatin for Stage III-IVB patients achieved significant benefit [35, 36].

To evaluate the benefit of the adjuvant phase, the trial by Chen et al. had randomized 508 patients to compare concurrent-alone CRT versus concurrent adjuvant CRT [37]. With a median follow-up of 38 months, preliminary report showed no significant improvement in 2-year failure-free survival (86% vs 84%). However, the hazard ratio was in favor of the concurrent-adjuvant arm (HR 0.74, 95% CI 0.49 – 1.10, p = 0.13) Similar trends were also observed for other endpoints (including OS, locoregional and distant control). Longer follow-up is needed to confirm the final conclusion. The second patient-data meta-analysis (MAC-NPC_2), with updated data from previous trials and inclusion of more randomized-controlled trials was published in 2015 [38]. A total of 4806 patients from 19 trials (Table 1) were included. The median follow-up duration was 7.7 years. Trials with concurrent-adjuvant chemotherapy and those with concurrent-alone chemotherapy were analyzed as distinct groups.

Table 1. Summary of eligible trials in the second MAC-NPC meta-analysis

Trial	Year of publication	Experimental (number of deaths/number entered)	Control (number of deaths/number entered)	Observed–expected	Variance	Hazard ratio (95% confidence interval)
Concurrent						0.80 (0.70-0.93)
PWHQEH-94	2005	92/174	101/176	-10.4	48.0	
QMH-95Conc	2004	25/56	24/55	0.0	12.2	
QMH-95Conc^{+}	2004	19/57	24/54	-4.9	10.6	
VUMCA-95 (unpublished)	NA	111/256	116/253	-6.4	56.6	
Guangzhou 2001	2013	21/59	31/56	-7.8	12.7	
Guangzhou 2002-02	2012	73/204	81/204	-2.2	38.5	
Guangzhou 2003	2011	9/116	26/114	-9.4	8.7	
Subtotal		350/922	403/912	-41.0	187.3	
Concurrent + adjuvant						0.65 (0.56-0.76)
INT-0099	1998	59/97	79/96	-22.8	33.0	
SQNP01	2005	60/111	72/110	-12.4	32.4	
NPC-9901	2010	69/172	93/176	-12.8	40.5	
NPC-9902CF	2011	22/51	18/42	-0.3	9.9	
NPC-9902AF	2011	15/44	29/52	-7.6	10.9	
Guangzhou 2002-01	2013	52/158	65/158	-10.9	29.0	
Subtotal		*277/633*	*356/634*	*-66.7*	*155.7*	
Induction						0.96 (0.80-1.16)
PWH-88	1995	15/37	13/40	1.8	6.9	

Table 1. (Continued)

Trial	Year of publication	Experimental (number of deaths/number entered)	Control (number of deaths/number entered)	Observed–expected	Variance	Hazard ratio (95% confidence interval)
Induction						
AOCOA	1998	54/167	55/167	-0.3	27.2	
VUMCA-89	1996	94/171	93/168	-0.2	46.7	
Japan-91	2002	17/40	20/40	-2.5	9.2	
NPC008	2009	12/34	14/31	-2.8	6.3	
HeCOG	2012	29/72	29/72	-0.1	14.5	
Subtotal		*221/521*	*224/518*	*-4.1*	*110.9*	
Adjuvant						0.87 (0.68-1.12)
TCOG-94	2002	52/80	53/78	-1.3	26.2	
QMH-95Adj	2004	24/54	24/55	0.8	12.0	
QMH-95Adj+	2004	19/57	25/56	-4.6	10.9	
Guangzhou 2006	2012	26/251	34/257	-3.6	15.0	
Subtotal		*121/442*	*136/446*	*-8.6*	*64.1*	
Total		**969/2518**	**1119/2510**	**-120.5**	**518.0**	**0.79 (0.73-0.86)**
Test for heterogeneity:		$p = 0.087$	$I^2 = 30\%$			
Test for interaction:		$p = 0.012$				
Residual heterogeneity:		$p = 0.36$				
Chemotherapy effect		$p < 0.0001$				

The result showed that addition of chemotherapy to RT improved OS (6% at 5 years and 8% at 10 years, HR 0.79, 95% CI 0.73 – 0.86). Only the subgroup composing of trials investigating concurrent-alone chemotherapy and the subgroup composing of trials on concurrent-adjuvant chemotherapy showed a significant improvement in both OS and PFS. Of special interest in this updated meta-analysis, the OS benefit at 5 years was 2.5% (95% CI -4.2 – 9.2%) by induction chemotherapy, 3.3% (95% CI -3.8 – 10.4%) by adjuvant chemotherapy, 5.3% (95% CI 0.8 – 9.8%) by concurrent-alone chemotherapy, and 12.4% (95% CI 7.0 – 17.8%) by concurrent-adjuvant chemotherapy.

This MAC-NPC dataset was further expanded to evaluate the best treatment option by means of network meta-analysis [39]. Both direct and indirect comparisons were conducted to estimate the relative efficacy between treatment modalities which have not been compared pairwise. A total of 5144 patients from 20 trials was included. The median follow-up duration of 7.4 years. The three treatments that had the highest effect on OS were concurrent-adjuvant CRT, concurrent-alone CRT and induction-concurrent CRT, with respective P-Scores of 96%, 70% and 63%, and corresponding benefit at 5 years of 12%, 8% and 6%. In comparison to radiotherapy alone, the HR for OS was 0.65 (95% CI 0.56 – 0.75) by concurrent-adjuvant CRT, 0.77 (95% CI 0.64 – 0.92) by concurrent-alone CRT and 0.81 (95% CI 0.63 – 1.04) by induction-concurrent CRT. The hazard ratio for OS showed a trend of in favor of concurrent-adjuvant chemotherapy over concurrent-alone chemotherapy (HR 0.85, 95% CI 0.68 – 1.05). The three best treatments for PFS were concurrent-adjuvant CRT, induction-concurrent CRT, and concurrent-alone CRT, with respective P-Score of 94%, 79% and 52%. The comparison on locoregional control showed that concurrent-adjuvant CRT was significantly better than concurrent-alone CRT [HR (95% CI) of 0.68 (0.48 – 0.98)], while the comparison on distant control showed that concurrent-alone CRT was inferior to induction-concurrent CRT [HR (95% CI) of 1.50 (1.03 – 2.19)].

Biomarker for Personalized Selection of Adjuvant Chemotherapy

There have been extensive studies in search of accurate biomarkers for diagnosis, treatment monitoring and prognostication for NPC. Plasma EBV DNA titer is an important biomarker that may contribute to refinement of prognosis and personalized selection of treatment strategy. Previous studies

have shown that baseline pre-treatment plasma EBV DNA titer is useful for predicting treatment failure and OS [17-22]. The study by Leung et al. suggested that among patients with stage I-II disease, those with high titer (>4000 copies) had poor prognosis similar to patients with advanced disease, particularly in terms of distant failure [22]. Hence, incorporation of this factor will be useful for selecting patients for chemotherapy.

The strongly significant prognostic value of post-treatment plasma EBV DNA has been consistently observed in many studies [23]. Chan et al. demonstrated that patients with post-treatment EBV DNA (>500 copies/ml) taken at 6-8 weeks after completion of concurrent CRT had significantly poorer PFS and OS than those with <500 copies/ml [24]. Lin et al. showed that patients with undetectable plasma EBV DNA taken at 1 week after completion of RT had significantly higher 2-year OS compared with those with persistently detectable titer (97% vs. 56%, $p < 0.001$) [17]. Similarly Le et al. showed that those who had post-treatment undetectable plasma EBV DNA at completion of RT had significantly higher 2-year OS compared to those who had post-treatment detectable titer (94% vs. 55%, $p < 0.002$) [20]. The Hong Kong NPC-0502 trial [NCT00370890] by Hui et al. similarly showed that undetectable plasma EBV DNA at 6 weeks after RT was the only independent prognosticator of relapse-free survival ($p = 0.0016$) and OS ($p = 0.0067$) [40].

However, the methodology of testing plasma EBV DNA has to be standardized and harmonized across different laboratories. In addition, the optimal timing for checking post-treatment plasma EBV DNA has yet to be defined, because it takes time for complete clearance of plasma EBV DNA after RT. A serial study by Lee et al. on 260 patients irradiated with IMRT showed that 30 patients still had persistently elevated plasma EBV DNA at 8 weeks after RT, but 20 patients had complete plasma EBV DNA clearance at later time points without evidence of relapse [41]. On the other hand, Twu et al. demonstrated that for patients with persistently elevated plasma EBV DNA taken at 1 week after completion of RT, addition of adjuvant chemotherapy using oral tegafur-uracil for one year could significantly improve 5-year PFS (63% vs. 29%, $p = 0.0037$) and OS (72% vs. 29%, $p < 0.0001$) [42]. Two on-going trials attempt to use post-treatment plasma EBV DNA for tailoring adjuvant chemotherapy. The Hong Kong NPC-0502 study randomized patients with detectable EBV DNA at 6 weeks after chemoradiotherapy to adjuvant chemotherapy using cisplatin-gemcitabine or observation [43]. The NRG-HN001 trial segregated patients into two risk groups based on EBV DNA at 6 weeks after concurrent cisplatin and IMRT [44]. Those with undetectable

EBV DNA are randomized to adjuvant chemotherapy using PF or observation to test whether adjuvant chemotherapy can be safely omitted in this low-risk group. Those with detectable EBV DNA are randomized to adjuvant chemotherapy using standard PF or paclitaxel-gemcitabine to test whether this new regimen is more potent for this high risk group. The results of these two trials are eagerly awaited.

INDUCTION-CONCURRENT CHEMORADIOTHERAPY

The strategy of induction-concurrent CRT is attractive because induction chemotherapy is much better tolerated than adjuvant chemotherapy. Furthermore, upfront chemotherapy may be more effective for eradicating micro-metastasis and shrinking the primary tumor for better coverage by subsequent RT. There are at least five randomized studies comparing induction-concurrent CRT versus concurrent-alone CRT, conflicting results have been reported [45-49]. Although the first report by Hui et al. (adding induction cisplatin and docetaxel, n = 65) showed a 26.5% improvement in 3-year OS by adding induction , there was no significant difference in PFS, and the initial gain in OS subsequently became negative with longer follow up as shown in the updated MAC-NPC meta-analysis [45]. Furthermore, both Fountzilas et al. 23 (adding cisplatin, epirubicin and paclitaxel, n = 141) and Tan et al. (adding carboplatin, gemcitabine and paclitaxel, n = 172) did not achieve survival benefit at 3-year [46, 47].

Two trials evaluating the addition of induction chemotherapy docetaxel, cisplatin and fluorouracil (TPF) to concurrent weekly cisplatin showed more encouraging results [48, 49]. The GORTEC 2006-01 trial was prematurely terminated due to slow accrual; only 83 Stage II-IVB patients had been randomized, early results by Daoud et al. reported significant improvement in both PFS and OS [48]. The trial from China (NCT01245959) accrued 480 Stage III-IVB patients, early results by Sun et al. showed significant improvement in 2-year failure-free survival and D-FFR. However, the median follow-up was only 21 months; longer follow-up is needed to evaluate the efficacy and late toxicity [49].

The trial by the Hong Kong NPC Study Group (NPC-0501 Trial) was the only trial that compared induction-concurrent CRT versus concurrent-adjuvant CRT using INT-0099 regimen as the standard arm [50]. A total of 803 patients