Neoadjuvant chemoradiation
followed by surgery for treatment of esophageal cancer

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Until now, surgery has been the cornerstone of curative treatment in patients with operable thoracic esophageal cancer.[1] Median survival of 13.6-15.2 months with 2-year survival rates of 34-37% were reported for patients treated with surgery alone.[2,3] One reason for the failure of local surgery alone is the fact that only 30-60% of patients are truly resectable at the time of diagnosis.

As an alternative to resection for locoregional treatment of esophageal cancer, there is some evidence to support combined definitive chemoradiation over radiotherapy (RT) alone.[4] With chemoradiation alone, a median survival time of 11 to 22 months was observed[5-7] and the 5-year survival rate reached 27% in a randomized study.[8] This figure is quite comparable to a surgical approach for locoregional carcinoma of the esophagus.[9] Patients who have technically unresectable local-regional carcinoma or those having a potentially resectable carcinoma but who are not fit for surgical resection are eligible to receive definitive chemoradiation.

The data from the first intergroup trial (RTOG85-01) compared the experimental treatment consisting of a total of four cycles (two during and two after radiation) of FU (1,000 mg/m2/d by continuous infusion for 4 days) and cisplatin (75mg/m2 day 1) plus 50 Gy of radiation therapy, and the control arm of 64 Gy of radiation alone. Survival was significantly better for patients treated with chemoradiation, 30% at 3 years and 26% at 5 years compared with 0% at 3 years in the radiation-alone treatment group.[4] An eight-year follow-up of this trial demonstrated an overall survival rate of 22% for patients receiving chemoradiation therapy.[10] Persistence of disease (despite therapy) was the most common mode of treatment failure; however, it was less common in the group receiving combined therapy (26%) than in the group treated with RT only (37%).[10]

The other study (EST 1282) also showed the survival benefit of chemoradiation (60Gy of RT plus concurrent mitomycin and 5-FU) over RT alone (60 Gy in 30 fractions).[11] Two- and 5-year survival rates were 12% and 7% in the RT alone arm and 27% and 9% in the chemoradiation arm. Patients treated with chemoradiation had a longer median survival (14.8 months), than patients receiving radiation therapy alone (9.2 months). This difference was statistically significant.

In an attempt to improve upon the results of RTOG 85-01, RTOG protocol 94-05, which randomized patients to the standard combined modality arm as in RTOG 85-01 (50.4 Gy of RT plus concurrent 5-FU and cisplatin) or high dose chemoradiation (64.8 Gy of RT plus concurrent 5-FU and cisplatin). A planned interim analysis using a stochastic curtailment analysis after 230 patients were accrued revealed that the chance of the high dose arm having a statistically superior survival result was only 2.4%. Therefore, the trial was closed before meeting its accrual goal of 298. This interim analysis suggested that chemoradiation with 64.8 Gy did not offer a survival benefit compared with standard dose radiation (50.4 Gy).[12] There was no significant difference in median survival (13.0 vs 18.1 months), 2-year survival (31% vs 40%), or local/regional failure and local/regional persistence of disease (56% vs 52%) between the high-dose and standard-dose arms. Data on randomized controlled trials of chemoradiation alone is summarized in table 1.

Other than radiation dose escalation, there is an endeavor of combining neoadjuvant chemoradiation followed by surgery to reduce the tumor size and maximize local control. The Federation Francophone de Cancerologie Digestive (FFCD trial 9102) carried out a randomized trial comparing chemoradiation alone versus chemoradiation followed by surgery in patients with esophageal cancer.[13] Eligible patients had operable T3N0-1M0 thoracic esophageal cancer. Staging was based on computed tomography (CT). Induction chemoradiation comprised of 2 cycles of fluorouracil (FU) plus cisplatin and either conventional (46 Gy in 4.5 weeks) or split-course (15 Gy, days 1 to 5 and 22 to 26) concomitant radiotherapy. For ethical reasons, only patients responding to induction chemoradiation were considered for the randomized part of the trial. In the absence of objective response or in case of contraindication to surgery, the treatment was decided by the investigator. If chemoradiation had not been tolerated,surgery was recommended. Of 444 eligible patients, 259 were randomly assigned to surgery (arm A) or continuation of chemoradiation (arm B; three cycles of FU/ cisplatin and either conventional [20 Gy] or split-course [15 Gy] RT)(Figure 1).

Table 1 summarizes studies comparing conventional radiation, definitive chemoradiation and elevated-dose chemoradiation

Study	Randomized	N	Histology (%)		RT dose	Daily dose	chemotherapy			Survival	MST
			SCC	Adeno	(Gy)	(Gy)	Drugs	Dosage (mg/sq.m)	Schedules		(months)
RTOG 85-01 (10)	RT alone	62	90	10	64	2				5Yr OS 0%	8.9*
	Chemo + RT	134	82	18	50	2	CDDP	100	1,29	5Yr OS 26%	12.5
							5FU	1000	1-4,29-32		
EST 1282 (11)	RT alone	60	100	0	60	2				5Yr OS 7%	9.2*
	Chemo + RT	59	100	0	60	2	Mitomycin	10	2	5Yr OS 9%	14.8
							5FU	1000	2-5,29-32		
RTOG 94-05 (12)	Chemo + RT 50.4	109	84	16	50.4	1.8	CDDP	75	1,29	2Yr OS 40%	18
	Chemo + RT 64.8	109	87	13	64.8	1.8	5FU	1000	1-4,29-32	2Yr OS 31%	13

Note : *p < 0.05

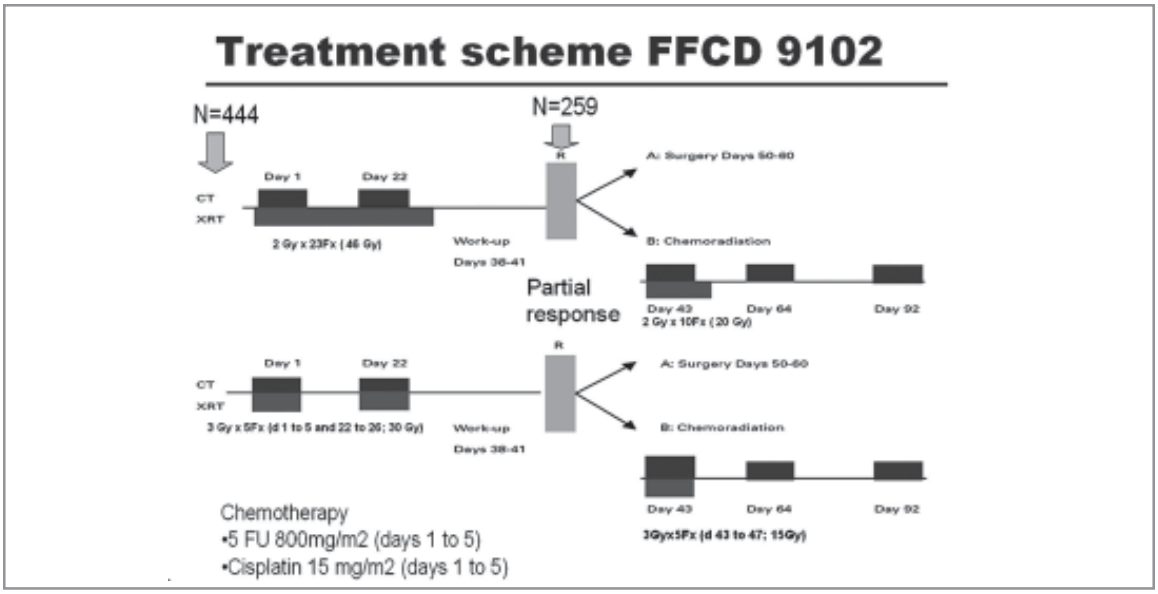


FIGURE 1 Schema of phase III study FFCD9102

Two-year survival rate was 34% in arm A versus 40% in arm B (P=0.44). Median survival time was 17.7 months in arm A compared with 19.3 months in arm B. Patients who did not respond to induction chemoradiation (i.e. did not randomized to arm A or B) were fared worse, with a median survival time of only 11.4 months. Two-year local control rate was 66.4% in arm A compared with 57.0% in arm B. The 3-month mortality rate was 9.3% in arm A compared with 0.8% in arm B (P = .002). The authors concluded that in patients with locally advanced thoracic esophageal cancers, especially epidermoid, who respond to induction chemoradiation, there is no benefit for the addition of surgery after chemoradiation compared with the continuation of additional chemoradiation. This study results were consistent with the results of the study by Stahl,[14] in which 172 patients with epidermoid esophageal cancer were randomly assigned to either induction chemotherapy (three cycles of bolus fluorouracil, leucovorin, etoposide, and cisplatin on days 1 to 3 every 3 weeks) followed by chemoradiation (40 Gy) followed by surgery (arm A), or the same induction chemotherapy followed by chemoradiation (at least 60 Gy) without surgery (arm B) (Figure 2). Overall survival at 2 years was equivalent between both treatment groups (39.9% in arm A vs 35.4% in arm B). Median survival time was also comparable (16.4 months in arm A vs 14.9 months in arm B). However, 2-year progression-free survival was better in arm A (64.3%) than in arm B (40.7%). Patients with tumor response to induction chemotherapy had a probability of surviving 3 years of more than 50%, regardless of the treatment group, whereas the outcome of nonresponders was generally poor (arm A: median survival, 9.1 months; 3-year survival

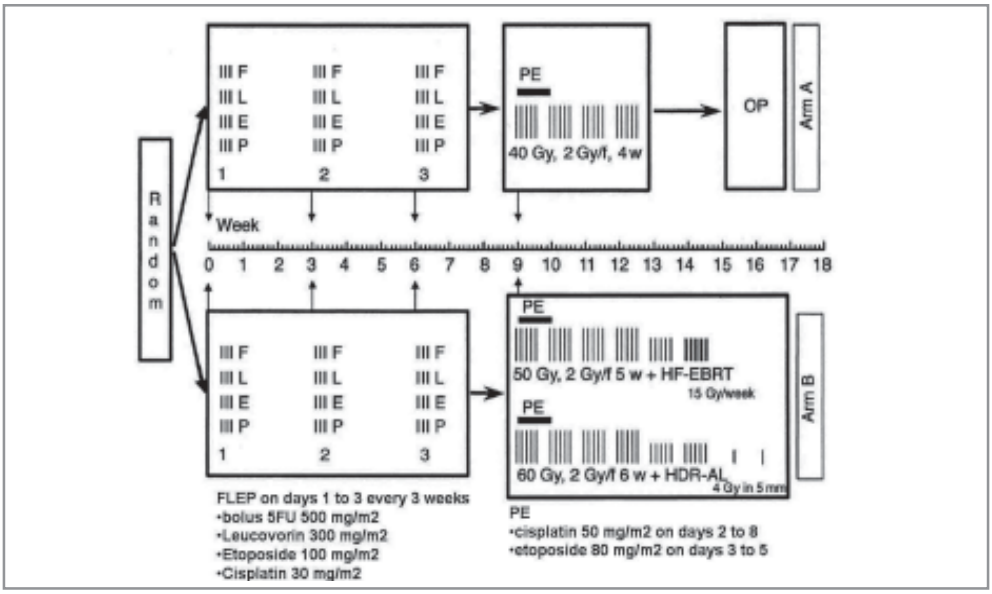


FIGURE 2 Schema of phase III study by Stahl

rate, 17.9%; arm B: median survival, 10.7 months; 3-year survival rate, 9.4%). From the data of above trials, it seems that patients with locally advanced squamous cell carcinoma of the intrathoracic esophagus who do not respond to induction chemotherapy or chemoradiation might benefit from salvage resection. Table 2 summarized the results of the above trials.

Neoadjuvant chemoradiation followed by surgery was also widely studied compared with surgery alone.[15-22] Bosset reported the result of a multicenter prospective randomized trial in which preoperative combined chemotherapy (i.e., cisplatin) and RT (37 Gy in 3.7 Gy fractions) followed by surgery was compared to surgery alone in patients with squamous cell carcinoma. There was no improvement in overall survival but a significantly higher postoperative mortality (12% vs. 4%) in the combined modality arm.[15] In contrary, in patients with adenocarcinoma of the esophagus, a single-institution phase III trial reported by Walsh, demonstrated a modest survival benefit (16 months vs. 11 months) for patients treated with induction chemoradiation therapy consisting of 5-FU, cisplatin, and 40 Gy (2.67 Gy fractions) plus surgery over resection alone.[16] CALGB 9781 was a prospective randomized Intergroup trial comparing surgery alone versus cisplatin (100mg/m2) and 5FU (1000 mg/m2/d x 4d) weeks 1 and 5 concurrent with radiation therapy (50.4 Gy- 1.8 Gy/fx over 5.6 weeks) followed by esophagectomy with lymph node dissection. Due to poor accrual, only 56 out of 500 patients were included in the study. Thirty patients were randomized to trimodality therapy and 26 to surgery alone. Median follow-up is 6 years. An intent- to- treat analysis showed a median survival of 4.5 yrs vs 1.8 years, while 5-year survival was 39% vs 16% in favor of trimodality therapy (logrank p=0.02).[17]

Table 2 summarizes studies comparing preoperative chemoradiation followed by surgery versus definitive chemoradiation alone

	FFCD 9102 [13]	Stahl [14]
Patients (n)	Intent-to-treat : 259	Intent-to-treat : 172
A:CT/RT->Sx	129	86
B:CT/RT	130	86
Inclusion criteria	Epidermoid (90%)	SCC (100%)
	Glandular (10%)	
	Thoracic esophagus	Thoracic esophagus (upper or mid)
	T3-4N0-1M0	T3-4N0-1M0
	Clinical eligibility for Sx or CT/RT	Good general condition + Lab
Exclusion criteria	Tracheobronchial involvement	Tracheobronchial involvement
	Visceral or SPC metas	
	Weight loss > 15%	
	Heart/Cirrhosis/Respiratory disease	
Workup	Gastroscope + Biopsy	Gastroscope + Biopsy
	Esophagogram	Esophagogram
	CT, EUS	CT, EUS
	Bronchoscope	
	SPC U/S	
Definition of	CR : No dysphagia/tumor in imaging	CR : Same
Tumor response	PR : > 30% decrease in length on esophagogram	PR : > 50% tumor regression CT and > 50% reduction of intraesophageal tumor extension as assessed by barium swallow.
Randomization	After response to CT/RT	At first
End point	OS	OS
	Hypothesis : Equivalence of 2yr OS	Hypothesis : Equivalence of 2yr OS
Chemotherapy	Concurrent : Cis/5FU (q 3) x II-III	Induction : 5FU/LV/Cis/Eto (q 3) x III 80% response, 20% Non response Concurrent : Cis/Eto x I
Radiation	Conventional RT	Conventional RT
	A : 46Gy/23F -> Sx	A : 40Gy/20F -> Sx
	B : 46Gy/23F -> Boost to 66 Gy/33F	B : 40Gy/20F -> Boost to 65+Gy/30F
	Split-course RT	
	A : 15Gy/5F q 3 wk x II (30Gy) -> Sx	
	B : 15Gy/5F q 3 wk x III (45Gy)	
Surgery	Transthoracic esophagectomy (94%)	Transthoracic esophagectomy (100%)
MST		
A	17.7 months	16 months
B	19.3 monsts	15 months
2Yr OS		
A	33.6%	39.9%
B	39.8%	35.4%
Local control		
A	2Yr local control 66.4%	2Yr PFS 64.3%
B	2Yr local control 57.0%	2Yr PFS 40.7%

The other trials showed conflicting results (table 3). A survival benefit with neoadjuvant chemoradiation has not been satisfactorily demonstrated since most of these trials were underpowered. Moreover,a major drawback with most of these trials is the inadequacy of the radiation dose to shrink bulky disease and to kill micrometastases. Most trials used low-to- moderate doses by current standard, partly because of the crude methods of radiation planning and delivery at that time, and the fear that higher doses might result in increased surgical morbidity. However, several meta-analyses have suggested that neoadjuvant chemoradiation is an appropriate treatment choice (table 4), and thus has been integrated into the standard treatment of patients with locally advanced, operable esophageal cancer (figure 3).

Urschel combined 9 randomized controlled trials which included a total of 1,116 patients.[23] Compared with surgery alone, neoadjuvant chemoradiation and surgery improved 3-year survival and reduced local-regional cancer recurrence. Odds ratio of neoadjuvant chemoradiation versus surgery alone were 0.66 (95%CI 0.47-0.92; P=0.016) for 3-year survival and 0.38 (95%CI 0.23-0.63; P=0.0002) for local-regional cancer recurrence. A complete pathological response to chemoradiation occurred in 21% of patients. Moreover, the 3-year survival benefit was most pronounced when chemotherapy and radiotherapy were given concurrently (OR 0.45, 95% CI 0.26 to 0.79, P = 0.005) instead of sequentially (OR 0.82, 95% CI 0.54 to 1.25, P= 0.36). The rate of adverse treatment events was not significantly different in the two patient groups, but there was a trend in favor of surgery alone for both operative mortality and all treatment mortality including anastomotic leakage and postoperative pulmonary complications.

Fiorica performed a meta-analysis of data from 6 randomized control trials, 764 patients, and showed that in resectable esophageal cancer, preoperative chemoradiation significantly improves three year survival as well as impressive tumor downstaging versus surgery alone.[24] There was evidence that chemoradiation significantly increased postoperative mortality but fewer patients need to be treated to benefit from the treatment than need to be treated to be harmed immediately post surgery. The effect of preoperative chemoradiation on overall survival was much more pronounced and statistically significant in patients with adenocarcinoma, however, the authors discussed that the sample size of this subgroup analysis was small (data obtained from only 2 trials), and caution must be exercised when interpreting results from this exploratory analysis.

Gebski identified 10 randomized studies from 1983 to 2006 including 1209 patients that compared neoadjuvant chemoradiation with surgery alone.[25] The hazard ratio for all-cause mortality with neoadjuvant chemoradiation versus surgery alone was 0.81 (95% CI 0.70-0.93;

Table 3 summarizes studies comparing preoperative chemoradiation followed by surgery versus surgery alone

Study	Randomized	N	Histology (%)		RT dose	Daily dose	chemotherapy			Survival	MST
			SCC	Adeno	(Gy)	(Gy)	Drugs	Dosage (mg/sq.m)	Schedules		(months)
Bosset[15]	CRT+S	151	100	0	Sequential 37	3.7	CDDP	80	0-2,19-21	3Yr OS 36%	18.6
	S	146	100	0						3Yr OS 34%	18.6
Walsh[16]	CRT+S	58	0	100	Concurrent 40	2.67	CDDP	75	7,42	3Yr OS 32%	16*
							5FU	15 mg/kg	1-5,36-40		
	S	55	0	100						3Yr OS 6%	11
CALGB 9781[17]	CRT+S	30	25	75	Concurrent 50.4	1.8	CDDP	100	1,28	5Yr OS 39%	4.5 Yr*
							5FU	1800	1-4,28-31		
	S	26								5Yr OS 16%	1.8 Yr
Burmeister[18]	CRT+S	128	35	65	Concurrent 35	2.33	CDDP	80	1	3Yr OS 33%	22.2
							5FU	1800	1-4		
	S	128	39	61						3Yr OS 27%	19.3
Urba[19]	CRT+S	50	26	74	Concurrent 45	1.5 bid	CDDP	20	1-5,17-21	3Yr OS 30%	16.9
							5FU	300	1-21		
	S	50	24	76			Vinblastine	1	1-4,17-20	3Yr OS 16%	17.6
Le Prise[20]	CRT+S	41	100	0	Sequential 20	2	CDDP	100	1,21	1Yr OS 47%	10
							5FU	600	2-5,22-25		
	S	45	100	0						1Yr OS 47%	10
Nygaard[21]	CRT+S	53	100	0	Sequential 35	1.75	CDDP	20	1-5,15-19	3 Yr OS 17%	9
							BLM	5	1-5,15-19		
	S	50	100	0						3Yr OS 10%	8.4
Apinop[22]	CRT+S	35	100	0	Concurrent 40	2	CDDP	100	1,29		10
							5FU	1000	1-4,29-32		
	S	34	100	0							10

Note : *p < 0.05

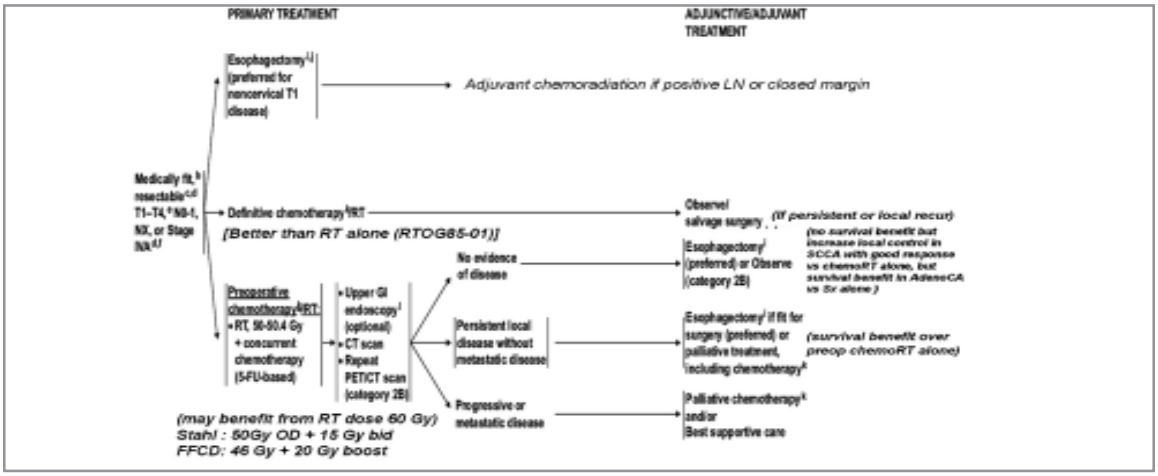
Table 4 summarizes meta-analyses comparing preoperative chemoradiation followed by surgery versus surgery alone

	Urschel[23] (95%CI)	Fiorica[24] (95%CI)	Gebski[25] (95%CI)
Number of trials	9	6	10
Number of patients	1116	764	1209
OR of 3 Yr OS	0.66	0.53	0.81
	0.47-0.92	0.31-0.93	0.70-0.93
OR of resection	2.5		
	1.05-5.96		
OR of downstaging		0.43	
		0.26-0.72	
OR of complete resection	0.53		
	0.33-0.84		
OR of operative mortality	1.72	2.1	
	0.96-3.07	1.18-3.73	
OR of all treatment mortality	1.63		
	0.99-2.68		
OR for local-regional recurrence	0.38		
	0.23-0.63		
OR for distant metastasis	0.88		
	0.55-1.41		
OR for all cancer recurrence	0.47		
	0.16-1.45		
Subgroup analysis			
3Yr OS Concurrent chemoRT	0.45		0.76*
	0.26-0.79		0.59-0.98
3Yr OS Sequential chemoRT	0.82		0.9*
	0.54-1.25		0.72-1.03
3Yr OS squamous cell carcinoma	0.75	0.81	0.84
	0.52-1.09	0.55-1.19	0.71-0.99
Mortality of adenocarcinoma		0.24	0.75
		0.07-0.78	0.59-0.95
Mortality of BED > 35Gy3		0.4	
		0.13-1.22	
Mortality of BED < 35Gy3		0.64	
		0.33-1.24	

*only squamous cell CA was analyzed

OR : odds ratio, neoadjuvant chemoradiation vs surgery alone (value <1 favor neoadjuvant chemoradiation)

FIGURE 3 NCCN guideline



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p=0.002), corresponding to a 13% absolute difference in survival at 2 years. The results for different histological tumor types were demonstrated in both squamous-cell carcinoma and adenocarcinoma. Subgroup analysis showed that the effect was slightly more evident in patients with squamous cell carcinoma who had concurrent treatment (hazard ratio for mortality 0.76 (95% CI 0.59-0.98)) rather than sequential treatment (hazard ratio for mortality 0.90 (95% CI 0.72-1.03)).

As radiation planning and delivery methods have improved over the past 15 years, there has been a tendency for increasing radiation dose. Current trials have used higher doses of radiation (typically 50 Gy) that are likely to result in better downstaging of overt tumors. RTOG carried out two phase II studies of induction chemotherapy followed by chemoradiation and surgery. It was hypothesized that induction chemotherapy prior to definitive chemoradiation may: (1) result in delay or elimination of micrometastases, (2) make chemoradiation more effective by diminishing the bulk of primary tumor, and (3) allow patients to receive all intended therapy because of improved tolerance to chemotherapy in the induction setting.

RTOG 0113 is a randomized phase II study comparing two non-operative therapeutic strategies using induction chemotherapy followed by concurrent paclitaxel-based chemotherapy and concurrent radiotherapy (50.4 Gy) in patients with local-regional esophageal and gastroesophageal junction carcinoma (figure 4).[26]

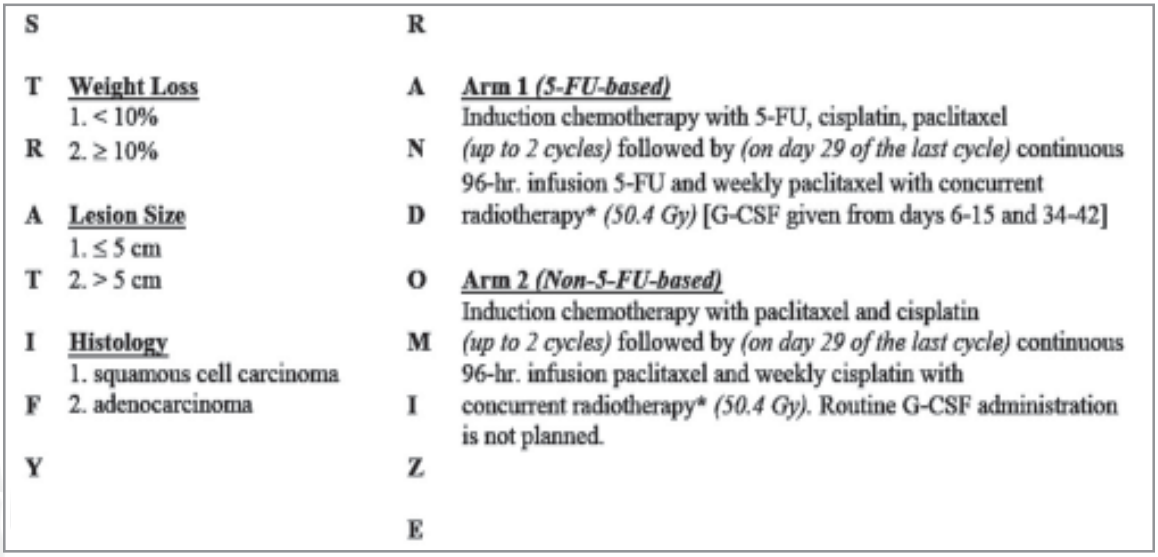

FIGURE 4 Schema of RTOG 0113

The 5-FU based arm and the non-5-FU based arm had 1-year overall survival rates of 75.7% and 66.7%, respectively, as compared to 66.0% for the historical control (RTOG 9405: 50.4 Gy with cisplatin and 5FU arm). Grade 4 toxicities (CTC 2.0) have been reported for 28% of patients on the 5-FU based arm and 38% of patients on the non-5-FU based arm, both were higher than the RTOG 9405. The authors concluded that although the therapeutic improvements are likely with the addition of induction cytotoxic agents, neither of the induction chemotherapy arms are recommended for phase III.

RTOG 0246 explored the feasibility and ability of induction chemotherapy with cisplatin, paclitaxel and 5FU followed by chemoradiation (cisplatin and 5FU concurrent with radiation 50.4 Gy) and selective salvage surgery.[27] The result is pending.

In conclusion, surgery remains the treatment of choice in early stage resectable esophageal cancer. Post-operative adjuvant chemotherapy with or with out radiation is justified in patients with closed margin or positive lymph node. For the patients with locally advanced or inoperable disease, either definitive chemoradiation or induction chemoradiation followed by surgery is appropriate treatment. Patients who do not respond to induction chemoradiation should undergo salvage surgery for survival advantage, while patients who respond well to induction chemoradiation still benefit from salvage surgery for better local control albeit no survival advantage.

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