



Cisplatin, 5-FU and Accelerated Hyperfractionation with Concomitant Boost Radiation Followed by Surgical Resection and Adjuvant Docetaxel for Patients Presenting with Locally Advanced Esophageal Carcinoma

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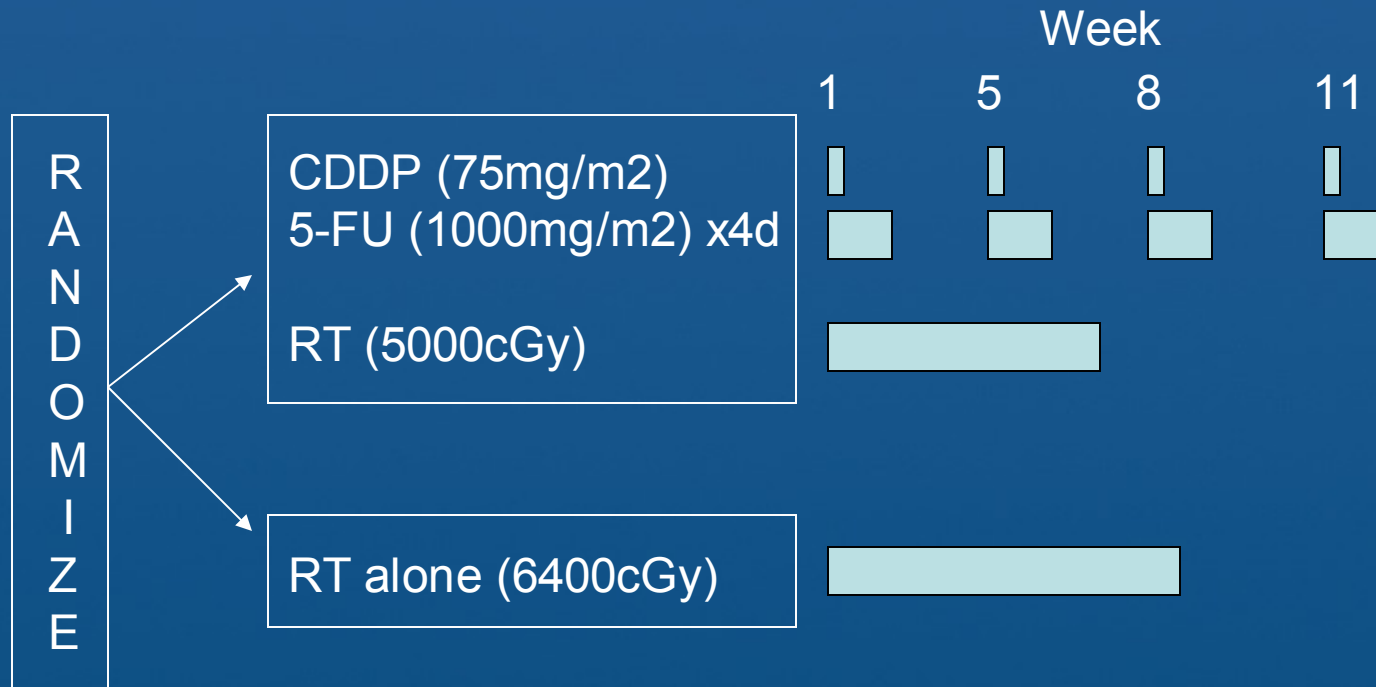
Historical Perspective

- Surgery had been the standard treatment especially for node negative individuals.
- Radiation therapy historically has been reserved for medically inoperable cases, or more advanced tumors.
- Earlam et al performed 2 separate meta-analyses:
 - 122 surgical papers with 83,783 patients with SCCa of esophagus
 - 49 RT papers with 8489 patients with

	Surgery alone	RT alone
2yr OS	20%	8%
5yr OS	12%	6%

Historical Perspective

RTOG 8501: RT vs Chemo/RT



RTOG 85-01: *RT vs Chemo/RT*

Time, y	No. (%) Alive Following Radiation Therapy Only (Randomized)	No. (%) Alive Following Combined Modality Therapy	
		Randomized	Nonrandomized
0	62 (100)	61 (100)	69 (100)
1	21 (34)	32 (52)	43 (62)
2	6 (10)	22 (36)	24 (35)
3	0 (0)	18 (30)	18 (26)
4	0 (0)	17 (30)	13 (19)
5	0 (0)	14 (26)	10 (14)
6	0 (0)	12 (22)	6 (10)†
7	0 (0)	12 (22)	2 (6)†
8	0 (0)	10 (22)	...
9	0 (0)	4 (20)†	...
10	0 (0)	3 (20)†	...
Total dead (median, mo)	62/62 (9.3)	48/61 (14.1)	65/69 (16.7)

At 3 years, no patient treated with RT alone survived

At 5 years, 26% of patients treated with chemo/RT survived

Nearly 50% of patients in chemo/RT arm still experienced some form of loco-regional failure!

Herskovic, *NEJM*, 326: 1393-1393, 1992
Cooper, *JAMA*, 281: 1623-1627, 1999

- Given high rates of local failures, adding surgery would seem like a reasonable addition to chemo/RT.
- 3 randomized trials comparing Surgery alone vs Trimodality Therapy:
 - University of Michigan (*Urba et al*)
 - EORTC (*Bosset et al*)
 - St. James Hospital (*Walsh et al*)

Trimodality: Univ. of Michigan

Urba, *JCO*, 19: 305-313, 2001

(median f/u 98mo)	Surgery alone	Trimodality	p-value
Median Survival	17.6mo	16.9mo	ns
3yr OS	16%	30%	0.15

Trimodality: EORTC

Bosset, *NEJM*, 337: 161-167, 1997

(median f/u 55mo)	Surgery alone	Trimodality	p-value
Median Survival	18.6 mo	18.6 mo	ns
3yr OS	34%	37%	0.78
3yr DFS	40%	28%	0.003
Postop Mortality	4%	12%	0.012

Trimodality: St. James Hospital

Walsh, *NEJM*, 335: 462-467, 1996

(median f/u 10mo)	Surgery alone	Trimodality	p-value
Median Survival	11 mo	16 mo	ns
3yr OS	6%	32%	0.01



Trimodality: Meta-analysis

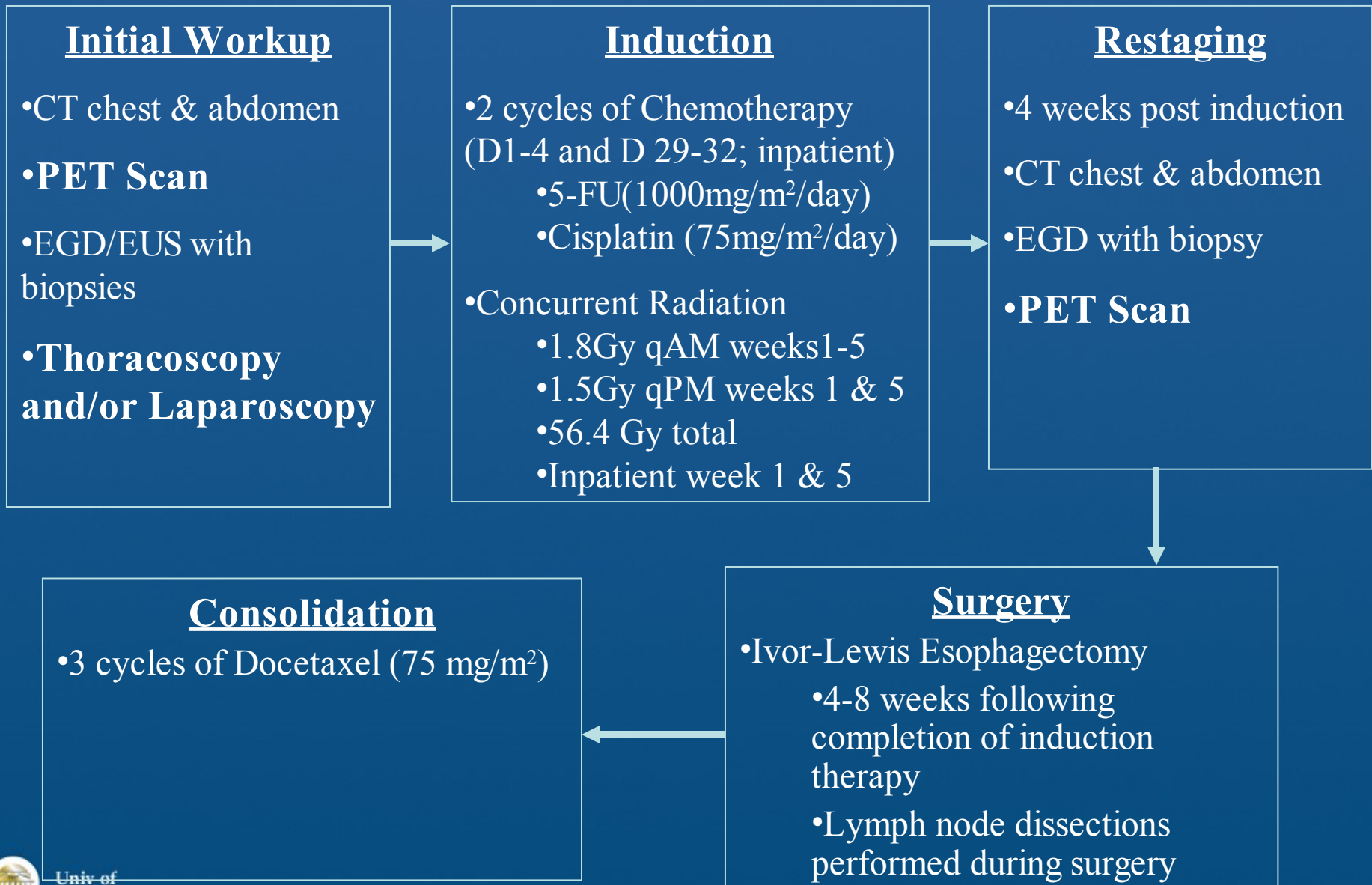
- 9 randomized, controlled trials involving 1,116 patients, comparing NCRT+Surgery versus Surgery alone
- Trimodality therapy associated with:
 - **improved** 3 year overall survival
 - **improved** local-regional recurrence
 - **improved** rate of resection
 - **improved** rates of complete resection (path CR-21%)
- Trimodality therapy associated with a trend towards :
 - **increased** operative mortality
 - **increased** anastomotic leaks
 - **increased** postop pulmonary complications



**The University of Maryland
Trimodality Approach to
Locally Advanced Esophageal Cancer:
UMGCC #9967**



The University of Maryland Trimodality Approach to Locally Advanced Esophageal Cancer: UMGCC #9967



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Patient Characteristics

Average Age (years)	59
Males	40
Females	9
Median KPS	90
Average Weight Loss (lbs)	14
Adenocarcinomas	37
Squamous Cell	12
GE Junction	25
Median f/u	22 mo

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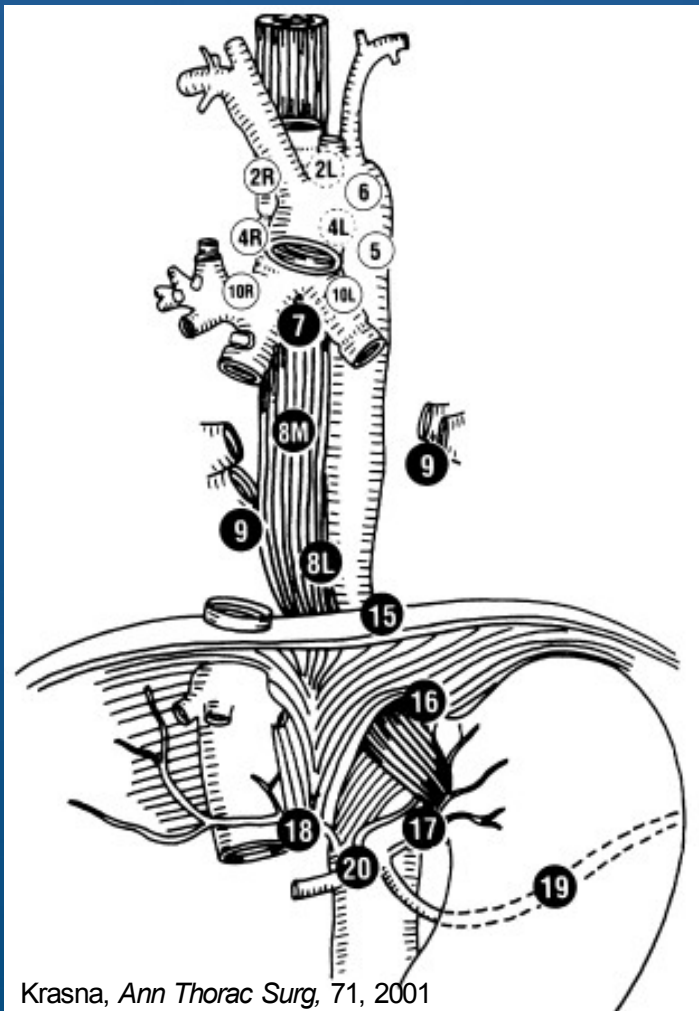
Surgical Stage

Stage IIA	$T_2N_0M_0$	1
	$T_3N_0M_0$	18
Stage IIB	$T_1N_1M_0$	1
	$T_2N_1M_0$	2
Stage III	$T_3N_1M_0$	14
Stage IVa	$T_2N_0M_{1a}$	1
	$T_3N_0M_{1a}$	4
	$T_2N_1M_{1a}$	1
	$T_3N_1M_{1a}$	7



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Thoracoscopic / Laparoscopic Staging



Krasna, *Ann Thorac Surg*, 71, 2001

LN Station	Incidence Sampled	Incidence Positive
Level 2	10%	0%
Level 3	20%	0%
Level 4	27%	2%
Level 5	27%	4%
Level 6	20%	4%
Level 7	71%	4%
Level 8	86%	12%
Level 9	61%	4%
Level 15	12%	2%
Level 16	31%	8%
Level 17	67%	20%
Level 18	8%	4%
Level 20	59%	18%



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Pre-Treatment Sensitivity & Specificity of PET

	Primary	Nodes
Sensitivity	98%	26%
Specificity	N/A	83%

Sensitivity = proportion of patients with disease who have positive test

Specificity = proportion of patients without disease who have negative test

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Toxicity of Induction Therapy

Leukopenia	Grade 3	16%
	Grade 4	4%
Neutropenia	Grade 3	6%
	Grade 4	6%
DVT	Grade 3	2%
	Grade 4	2%
	Grade 5	2%
Dysphagia	Grade 2	20%
	Grade 3	2%
	Grade 4	0%
Death NOS	Grade 5	2%

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- 6 of 49 patients were not taken to OR:
 - 2 for medical reasons
 - 2 had metastases on restaging scans
 - 1 died of unknown causes 3 weeks after chemo/RT
 - 1 died of pulmonary embolism 1 week after chemo/RT
- 43 of 49 patients taken to OR:
 - 2 had liver/peritoneal mets; resection aborted
 - 41 had complete esophagectomy

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Surgical Complications	# patients	Led to Death
Anastomotic Leak	10	2 deaths
Ischemic Bowel	2	2 deaths
Myocardial Infarction	1	1 death
Respiratory Failure	1	1 death
Fistula Formation	3	--
Pulmonary Embolism	1	--
Atrial fibrillation	2	--
Pleural Effusion	1	--



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Primary only	
Complete Response	49%
Partial Response	51%
macroscopic	34%
microscopic	17%
Nodes only	
pN0	78%
pN+	22%
Overall Response (primary & nodes)	
Complete Response	49%
Partial Response	51%

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Post-Induction ability of PET to detect disease

	Primary	Nodes
Sensitivity	66%	0%
Specificity	50%	91%
PPV	59%	0%
NPV	58%	78%

Sensitivity = proportion of patients with disease who have positive test

Specificity = proportion of patients without disease who have negative test

PPV = proportion of patients testing positive who actually have disease

NPV = proportion of patients testing negative who do not have disease

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Ability to Deliver Adjuvant Chemo

- 35 surgical patients eligible to receive adjuvant docetaxel
 - 2 patients refused chemo
 - 3 patients had progressive disease
 - 3 patients not given due to medical reasons
- 23 (85%) received all 3 cycles after surgery

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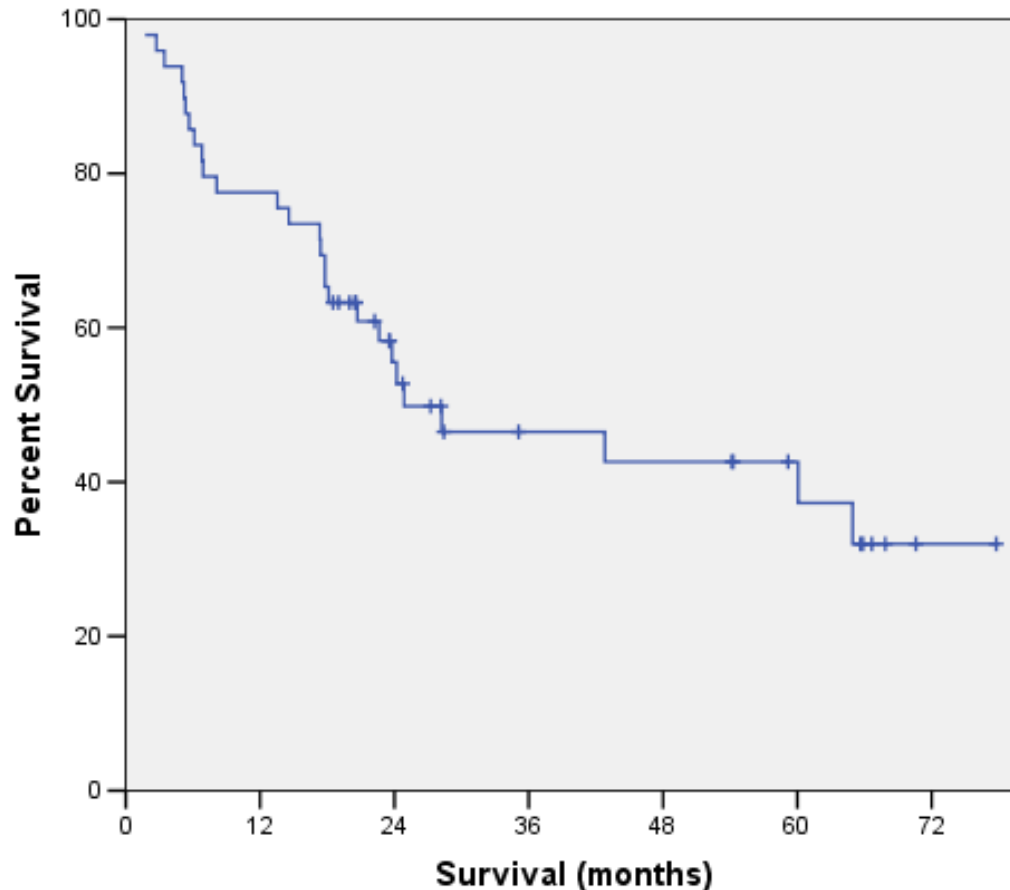
Median follow-up: 22 months

Initial Failure Patterns:

Treatment-related death	8	16%
Local Recurrence	0	0%
Nodal Recurrence	2	4%
Distant Mets	14	29%
Nodal + Distant	2	4%
No Failure	23	47%
Total	49	100%

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Overall Survival of Entire Cohort (49 patients)



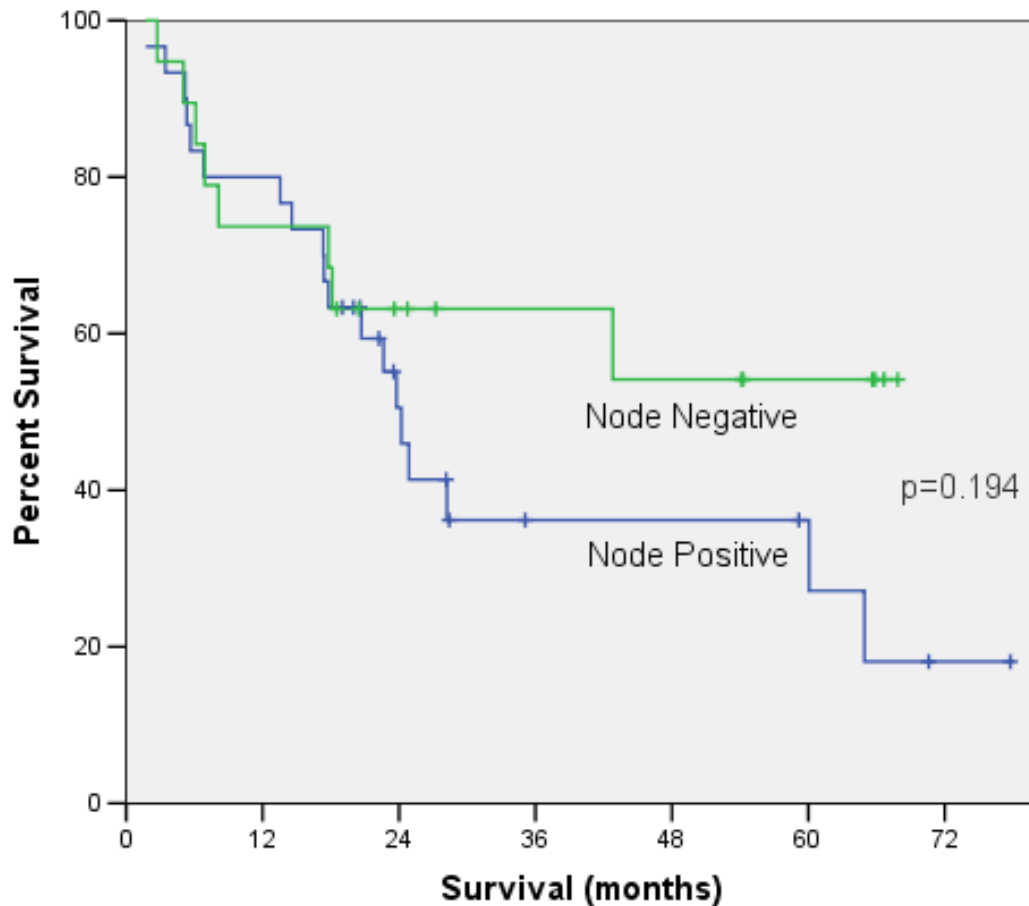
MS	25 months
1yr OS	78%
2yr OS	56%
3yr OS	47%
5yr OS	37%

Of the patients who underwent surgery (n=41), MS was 60 months, and 3yr OS was 55%



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Overall Survival based on Pre-Therapy Nodal Status



	Pretreatment	
	N0	N+
MS	Not reached	24 mo
1yr OS	74%	80%
3yr OS	63%	36%
5yr OS	54%	27%

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- There was no difference in OS when comparing pathologic response of primary alone, nodes alone, or primary and nodes combined.
- This effect may be due to adjuvant docetaxel.
- So, how did we stack up to the randomized trials?

	Univ of Michigan	EORTC	St. James	UMGCC 9967
MS	17mo	19 mo	16 mo	25 mo
3yr OS	30%	37%	32%	47%

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Conclusions

3. Cisplatin, 5-FU and accelerated hyperFx w/ concomitant boost RT as induction therapy achieved pCR in nearly 50% of patients.
5. However, this trimodality protocol was associated with 16% mortality (mostly surgical).
7. Despite a high mortality, this approach along with adjuvant docetaxel achieved a MS of 24 months and 3yr OS of 47%.

Future Directions

- Improve responses with more active systemic agents
- Improve therapeutic ratio
 - Intensifying radiation therapy while decreasing toxicity
 - Dose escalation
 - Target delineation, especially involved nodes
- Optimize the role of surgery
 - Surgical salvage?

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