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"Low-Maruyama-Index" Surgery For Gastric Cancer A Blinded Re-analysis of the Dutch D1-D2 Trial

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ABSTRACT

A quantitative estimate of residual nodal disease after gastric cancer surgery, the "Maruyama Index of Unresected Disease" (MI), proved a strong independent predictor of survival in a large U.S. adjuvant chemo-radiation study in which surgical under-treatment was frequent. Data from the Dutch D1-D2 Lymphadenectomy Trial permits an opportunity to assess the prognostic value of this variable in a cohort with lower-stage disease treated with minimum D-1 lymphadenectomy and no adjuvant chemoradiation. Methods: Blinded to survival, and excluding those cases with missing information, MI could be calculated for 648 of the original 711 patients treated with curative intent. Survival was assessed by log rank and multivariate Cox regression analysis. All cases have been followed for a minimum of 11 years. Results: Overall Dutch Trial findings were not impacted by the absence of 63 cases with incomplete data. As expected, median MI was 26, much lower than in the previous U.S. study. In contrast to D level, MI < 5 proved a strong predictor of survival by both univariate and multivariate analysis. MI was an *independent* predictor of both overall survival (p= 0.016, HR=1.45, 95% CI 1.07-1.95) and relapse risk (p= 0.010, HR=1.72, 95% CI 1.14-2.60). Strong "dose-response" with respect to MI and survival was also observed. Conclusions: We conclude that in this trial, "low-Maruyama-index" surgery is associated with enhanced survival, whereas, outside of certain sub-groups, routine D-2 lymphadenectomy is not. This observation suggests that surgeons might better impact on patient survival by achieving a "low-Maruyama-index" operation rather than a particular d-level.

INTRODUCTION

Intergroup 0116 (SWOG 9008) , a two-armed prospective, randomized multi-center North American trial, established the value of postoperative, 5-FU-based, adjuvant chemo-radiotherapy for gastric cancer patients with sufficient caloric intake, good performance status, and adequate organ function.[1] While this conclusion has been questioned for certain subgroups, such as UICC Stage I-B cases, [2] and, more recently, cases with diffuse histology,[3] such adjuvant chemo-radiotherapy is now considered standard in North America.

Data elements capturing the extent of surgery and the extent of lymphadenectomy for Intergroup 0116 patients were meticulously collected and analyzed prior to any survival analysis. Although printed trial materials recommended D2 lymphadenectomy and included appropriate instructions, the extent of surgery was not mandated beyond the requirement that all margins of resection be negative and there be no identifiable residual disease. The nature of postoperative registration largely thwarted effective communication of such surgical recommendations, and the trial captured existing patterns of surgical care in North America during the accrual period, 8/'91 - 7/'98. Disappointingly, 54% of cases had less-than-D-1 lymphadenectomy ("D-0 lympghadenectomy"), and only 10% underwent D-2-or-greater lymphadenectomy.[1, 4] Critics of the trial emphasize it might have been positive because of high average burden of unresected regional nodal disease.[2]

Anticipating this possibility while the trial was still accruing, and funding a separate study to assess potential survival impact, one of the authors (S.H.) attempted to quantify the likelihood of unresected nodal disease for each INT 0116 patient by defining a so-called "Maruayama Index of Unresected Disease" or "Maruyama Index" (MI).[4] To calculate MI, the "Maruyama Computer Program" [5] was used to estimate the percentage likelihood of nodal involvement for each "regional" lymph node station left in situ by a given patient's surgeon. For the purpose of this analysis, "regional" was defined as in JRSGC [6] node stations #1 through #12 (see Figure 1). For the benefit of those unfamiliar with this tool, the "Maruyama Computer

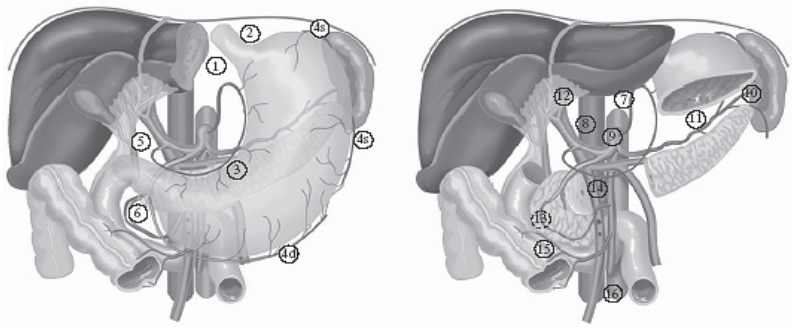


Figure 1. Defined lymph node stations. Stations #1-#16 are defined by the Maruyama Program. Stations #1-#12 are deemed "regional" and used for "Maruyama Index of Unresected Disease" (MI) calculations.

Program" [5] simply matches a given case with very similar cases previously treated at the National Cancer Center Hospital in Tokyo. The large number of cases in the N.C.C. Tokyo data base (3,843 cases, and recently expanded [7]) serves to make the nodal predictions of this computer program very accurate, not only for Japanese cases, but for cases from Germany and Italy as well.[5, 8, 9]. The "Maruyama Index of Unresected Disease" or "Maruyama Index" (MI) is defined as simply the sum of regional nodal disease percentages for "regional" node stations (#1-#12) not removed by the surgeon. Prior to any survival analysis, it was predicted that those with MI<5 would enjoy higher survival.

Despite differences in median survival (i.e. 27 months for D-0, 29 months for D-1, and 48 months for D-2), d-level failed to prove a significant predictor of survival in Intergroup 0116. However, in contrast to d-level, "Maruyama Index of Unresected Disease" (MI) proved, on both

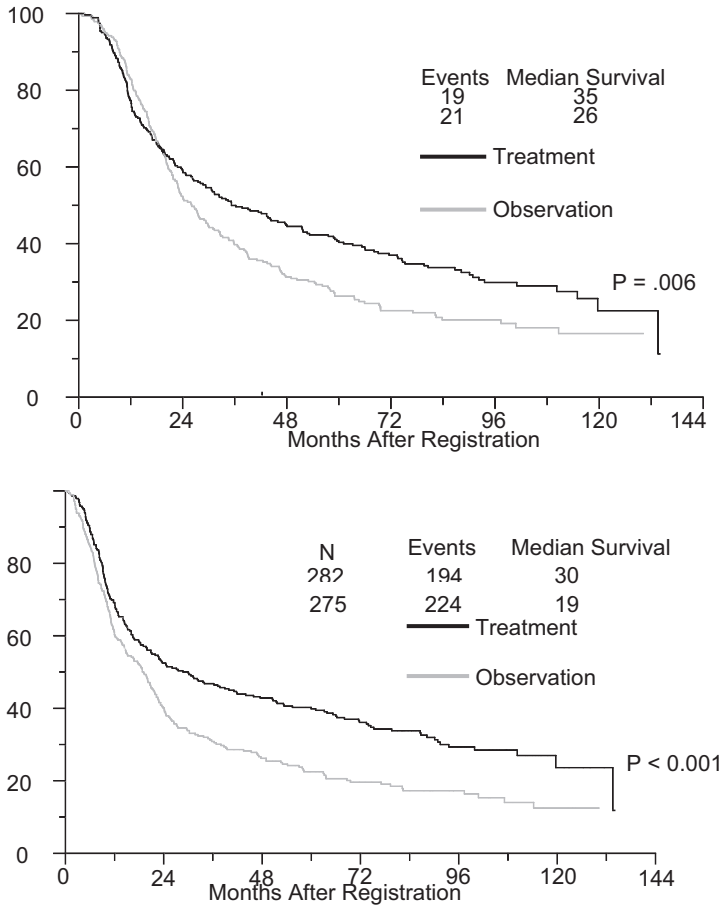


Figure 2. Updated overall survival curves for Intergroup 0116 chemoradiation cases. Overall survival (a) and relapse-free survival (b). Data kindly provided by the Southwest Oncology Group (see references 4 and 10)

univariate analysis (see updated survival curves in Figure 2a and 2b) and multivariate analysis to be a significant predictor, with a dose-response effect also noted. For cases with MI < 5 vs. MI ≥ 5, median overall survival was 87 months vs. 27 months (p=0.005). Median relapse free survival was 87 vs. 20 months (p=0.001). With T, N, and treatment group as covariates, hazard ratio was 1.9 for overall survival (95% CI 1.3-2.8) and was 2.0 for disease-free survival (95% CI 1.4-2.9).[4, 10]

Each case in the Dutch D1-D2 Trial has now been followed for a minimum of 11 years. Outside certain subgroups, (e.g. the subgroup with N-2 disease) the trial remains negative overall.[11] Compared to cases in the Intergroup Trial, cases in the Dutch Trial had generally lower-stage disease and also received more adequate surgical treatment. For example, 69% of Dutch cases were node-negative, versus only 15% in the Intergroup cases. Additionally, all but 137 (non-compliant) cases of the 711 treated for cure in the Dutch Trial received at least a D1 lymphadenectomy. Finally, none of the cases received adjuvant postoperative therapy. These facts, combined with the detailed lymphadenectomy data collected for each Dutch D1-D2 Trial participant, made Maruyama Index analysis attractive. We now report a blinded post hoc analysis of the impact of MI on survival and recurrence in this trial.

METHODS

Entry criteria, informed consent, randomization, surgical treatment, and quality control for the Dutch D1-D2 trial have been reported previously.[12, 13]

In the late 80's, Dr. K. Maruyama and colleagues at the National Cancer Center Hospital in Tokyo created a computer program (known as the "Maruyama Program") which searched their meticulously-maintained 3,843-patient database of gastric cancer cases treated by extensive lymphadenectomy, matching cases with similar characteristics to a given case. With seven demographic and clinical inputs (all identifiable pre-operatively or intra-operatively), the program predicts the statistical likelihood of nodal disease for 16 (JRSGC-defined [6]) nodal stations around the stomach (see Figure 1). Maruyama Program predictions have been assessed in Japan, Germany, and Italy, and found to be highly accurate.[5,8,9] The original version of the Maruyama Program was used for the Intergroup-0116 analysis. A CD-ROM with expanded case volume has recently been released,[7] and this was used for all but 19 of the MI calculations in the current study.

As noted in the introduction, the *"Maruyama Index of Unresected Disease" (MI)* has been defined (by author SH) as *the sum of Maruyama Program predictions for those regional node stations (stations #1-#12) left in situ by the surgeon*.[4] An identical definition was used for this study.

Data sufficient for MI calculation was available for 648 of the original 711 cases resected for cure in the Dutch D1-D2 Trial, and these constitute the basis for this study.

Table 1. Surgical and pathological characteristics by D-level of 648 Dutch Trial cases after excluding those cases with missing information for the calculation of "Maruyama Index of Unresected Disease" (MI). Distribution by D-level of lymphadenectomy. Percentages in parentheses. Statistics: Pearson Chi-square.

	D1	D2	P-value
Site of tumor			
Proximal	32 (50.8)	31 (49.2)	
Middle	96 (53.9)	82 (46.1)	0.967
Distal	181 (52.8)	162 (47.2)	
Diffuse	35 (54.7)	29 (45.3)	
Type of gastrectomy			
Distal/subtotal	237 (55.8)	188 (44.2)	0.059
Total	107 (48.0)	116 (52.0)	
T stage			
T1	91 (54.2)	77 (45.8)	
T2	164 (53.4)	143 (46.6)	0.272
T3	86 (53.4)	75 (46.6)	
T4	3 (25.0)	9 (75.0)	
N stratum (UICC 1997)			
N0	150 (54.2)	127 (45.8)	
N1 (1-6 nodes positive)	123 (53.0)	109 (47.0)	0.101
N2 (7-15 nodes positive)	47 (54.0)	40 (46.0)	
N3 (≥16 nodes positive)	14 (35.9)	25 (64.1)	
M1	10 (76.9)	3 (23.1)	
UICC stage			
IA	69 (53.1)	61 (46.9)	
IB	84 (55.6)	67 (44.4)	
II	88 (54.3)	74 (45.7)	0.428
IIIA	54 (51.9)	50 (48.1)	
IIIB	24 (60.0)	16 (40.0)	
IV	25 (41.0)	36 (59.0)	

Paralleling the previous Intergroup analysis, an MI cutoff of 5 was used for the initial univariate survival analysis.

For statistical analysis the SPSS programme was used. A p-value of 0.05 was considered statistically significant. Overall survival was calculated from the day of randomisation until either day of death (event) or day of last follow-up (censored). Relapse was also calculated from the day of randomisation. Data for a patient was censored when at last follow-up contact the patient was alive with no evidence of disease or had died of non-neoplastic cause without evidence of recurrence. Distribution by D-level was assessed by Pearson Chi-square. Distribution by MI was assessed by the non-parametric Kruskal-Wallis test. Survival and relapse risk was assessed by log rank and multivariate Cox regression analysis.

All cases were followed for 11 years or more.

RESULTS

Median age of the 648 cases was 66 years. Fifty-six percent were male. Distribution according to D-level by tumor site, T-stage, nodal stratum, type of gastrectomy, and UICC stage largely paralleled that of the originally reported 711 patients (Table I).[12]

As shown in Table 2, overall median MI for the 648 cases was 26. Median MI generally increased with advancing UICC stage, number of nodes positive, T-stage, D-level, and tumor involvement of overlapping sites, in that order. Tumors involving overlapping gastric sub-

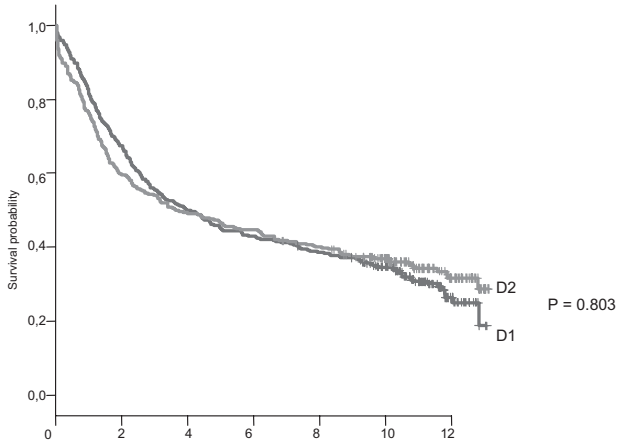
Table 2. Maruyama Indices according to surgical and pathological characteristics. Percentages in parentheses. Statistics: Non-parametric testing according to Kruskal-Wallis

Variable	N	Median MI	Range	Interquartile range	P-value
Overall	648	26	0 – 350	5 – 70	
Site of tumor					
Proximal	63 (9.7)	20	0 – 220	6 – 50	
Middle	178 (27.5)	23	0 – 350	4 – 74	0.026
Distal	343 (52.9)	24	0 – 228	5 – 64	
Diffuse	64 (9.9)	63	0 – 286	19 – 131	
Type of resection					
Distal/subtotal	425 (65.6)	21	0 – 228	4 – 64	0.060
Total	223 (34.4)	33	0 – 650	8 – 80	
Randomisation					
D1	344 (53.1)	50	0 – 350	12 – 100	<0.001
D2	304 (46.9)	10	0 – 228	0 – 35	
T stage					
T1	168 (25.9)	2	0 – 54	0 – 9	
T2	307 (47.4)	35	0 – 220	10 – 63	<0.001
T3	161 (24.8)	86	0 – 350	37 – 141	
T4	12 (1.9)	67	0 – 228	25 – 129	
Number of positive nodes					
N0	277 (42.7)	11	0 – 220	1 – 50	
N1 (1-6 nodes positive)	232 (35.8)	35	0 – 350	6 – 74	<0.001
N2 (7-15 nodes positive)	87 (13.4)	40	0 – 243	19 – 105	
N3 (≥16 nodes positive)	39 (6.0)	42	0 – 280	16 – 76	
M1	13 (6.0)	92	3 – 217	17 – 134	
UICC stage					
IA	130 (20.1)	2	0 – 54	0 – 8	
IB	151 (23.3)	24	0 – 199	8 – 62	
II	162 (25.0)	37	0 – 220	10 – 75	<0.001
IIIA	104 (16.0)	61	0 – 350	25 – 102	
IIIB	40 (6.2)	107	7 – 243	27 – 157	
IV	61 (9.4)	50	0 – 280	17 – 87	

sites (i.e. "diffuse" site) had a median MI of 63, significantly higher than for more localized tumors (P=0.03). Median MI was also higher for D1 cases (MI= 50 vs. 10, P=0.01).

Unsurprisingly, D1 and D2 survival curves for the 648 case cohort are similar (Figure 3).

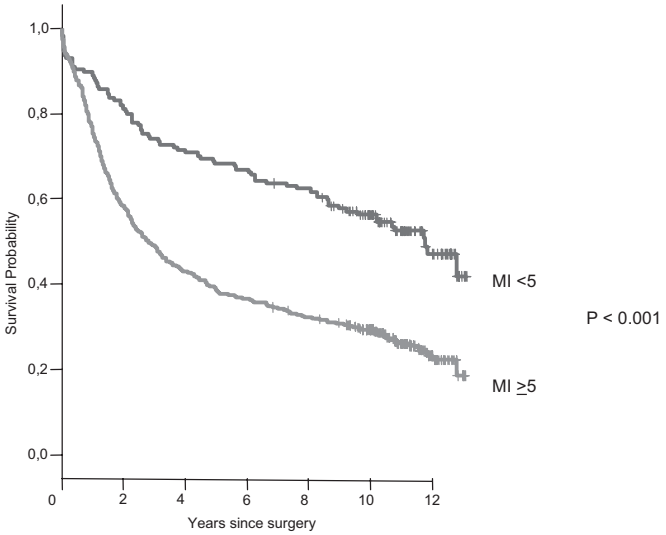
Only 154 cases had MI < 5. Overall survival (Figure 4) appears higher and relapse risk lower (not shown) for these cases (p<0.001 by log rank test for both comparisons).



No. at risk

D1	344	213	164	145	130	97	20
D2	304	173	146	132	116	86	32

Figure 3. Overall survival for 648 cases according to D-level randomization



No. at risk

MI<5	154	120	108	101	92	68	25
MI≥5	494	266	203	176	154	115	27

Figure 4. Overall survival for 648 Dutch Trial cases, according to MI <5 vs. MI >=5 status

Table 3. Multivariate Cox regression analysis of overall survival for 648 cases

Variable	Hazard ratio	95% CI	P-value
MI (<5 vs ≥5)	1.45	1.07 – 1.95	0.016
T stage			<0.001
T1	1.00		
T2	1.23	0.91 – 1.67	0.171
T3	1.87	1.33 – 2.65	<0.001
T4	2.22	1.15 – 4.29	0.018
N stratum (UICC 1997)			<0.001
N0	1.00		
N1	1.96	1.55 – 2.48	<0.001
N2	2.74	2.02 – 3.71	<0.001
N3	4.53	3.03 – 6.76	<0.001
M1	3.86	2.00 – 7.43	<0.001
Randomisation			
D1	1.00		
D2	0.95	0.77 – 1.16	0.610
Residual tumour			
R0	1.00		
R1	2.14	1.54 – 2.97	<0.001
Age	1.04	1.04 – 1.03	<0.001

Mutivariate Cox regression analysis reveals hazard ratios for overall survival as depicted in Table 3 and for disease-free period as depicted in Table 4. In contrast to D-level, MI was a significant independent predictor of overall survival and disease-free interval.

Overall survival (Figure 5) and relapse risk (not shown) by MI quartiles indicate what may be termed a "dose-response" effect with respect to likelihood of residual nodal disease as estimated by MI. Survival is highest for the low MI quartile and poorest for the high-MI quartile.

DISCUSSION

Median MI for the 648 cases in this study is 26. For cases in the previous Intergroup Trial, it was 70. This is not surprising given the 54% D0 rate in the latter study.[1, 4]

Nodal staging in this study is more accurate than for Intergroup Trial cases. More nodes were resected and pathological assessment of these nodes was more detailed.[12, 13]

The relationship between MI, T-stage, nodal stratum, and UICC stage is complicated. If one hypothetically holds the extent of lymphadenectomy constant, higher-stage, more advanced tumors will tend to have a higher likelihood of disease in un-dissected regional node stations and, therefore, a higher MI. Such linkage with T-stage and nodes positive potentially biases the analysis against significance for MI in a multivariate analysis. Nevertheless, in multivariate

Table 4. Multivariate Cox regression analysis of disease free period for 648 cases

Variable	Hazard ratio	95% CI	P-value
MI (<5 vs ≥5)	1.72	1.14 – 2.60	0.010
T stage			<0.001
T1	1.00		
T2	2.06	1.28 – 3.21	0.003
T3	3.24	1.95 – 5.40	<0.001
T4	4.25	1.90 – 9.51	<0.001
N stratum (UICC 1997)			<0.001
N0	1.00		
N1	3.98	2.82 – 5.62	<0.001
N2	5.39	3.60 – 8.08	<0.001
N3	9.10	5.56 – 14.89	<0.001
M1	6.69	3.18 – 14.06	<0.001
Randomisation			
D1	1.00		
D2	1.15	0.89 – 1.48	0.279
Residual tumor			
R0	1.00		
R1	2.44	1.72 – 3.47	<0.001
Age	1.01	1.00 – 1.02	0.041

Cox regression analysis, correcting for T and N, MI remains a strong independent predictor of survival and relapse-free survival. When MI is divided in quartiles, as depicted in Figures 5, there is clear and significant "dose-response" with respect to survival and relapse risk. This further supports the prognostic value of MI.

D-level derives from the detailed and somewhat complicated Japanese Research Society for Gastric Cancer (JRSGC) definitions of nodal levels.[6] This scheme assigns, based on tumor location, a nodal level (N-1 through N-4) for each defined nodal station around the stomach, upper abdomen, and pera-aortic areas. In a D1 lymphadenectomy, all N-1 level node stations are removed, but not all N-2 level node stations. In a D2 dissection, all N-1 and N-2 nodal stations are removed, but not all N-3 nodal stations. D3 and D4 dissections are similarly defined. In general, all JRSGC N1 and most N2 nodal stations are considered "regional" by North American surgeons, and N3 and N4 nodes are generally considered "extra-regional." MI is calculated according to: a) the status (dissected or undissected) of "regional" node stations #1-#12; b) the Maruyama Program prediction of disease in any of the nodes of that station (i.e. percent likelihood of disease); and c) whether or not the surgeon has dissected the station. Worldwide, because gastric cancer is now staged according to UICC/AJCC TNM definitions, surgeons - particularly Western surgeons - not thoroughly familiar with the complicated JRSGC system have difficulty precisely defining which node stations need to be dissected for a "D1" or "D2" lymphadenectomy. In contrast, running the Maruyama Program either pre-

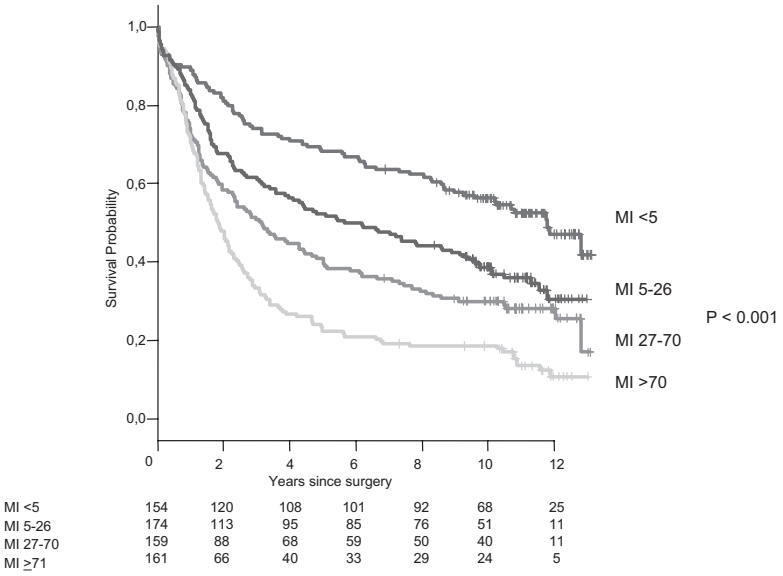


Figure 5. Overall survival for 648 Dutch Trial cases, by MI quartile. A "dose response" for estimated unresected disease, as quantified by MI, is evident

operatively or intra-operatively, and seeing visual and tabular output for quantified risk of disease in all defined regional nodal stations[7] is probably easier in the era when laptop computers and PC computers are available in most operating room suites.

Moveover, three separate prospective, randomized trials of D-1 versus D-2 lymphadenectomy have failed to show consistent value for routine use of more-extensive D2 lymphadenectomy.[12, 14, 15] Three additional trials of routine total gastrectomy, with or without extensive lymphadenectomy, have failed to show improved survival.[16-18] Scant data concerning results with D-0 lymphadenectomy are available because most experts consider this inadequate surgical treatment.

Despite the enormous expertise and experience involved in their derivation, the JRSGC definitions for N-level and D-level are arbitrary. In contrast, Maruyama Program output reflects actual experience with actual tumors of precisely matched characteristics, drawn from a staggeringly large data base. As noted, previous work has shown Maruyama Program predictions to be quite accurate.[5, 8, 9]. Surgeons adhering to the time-honored concept of trying to match the extent of surgical resection with the extent of regional disease should find the Maruyama Program a useful tool. In any case, the arbitrary and complicated, "D-level," JRSGC approach has not proven helpful.[11, 12, 14-18]

Both the MRC and Dutch Trials document that in European patients, JRSGC-defined D2 dissections (i.e. more extensive - but arbitrarily-defined – node dissections) are associated with significantly higher 30-day and in-hospital postoperative mortality (13% vs. 6.5% for the MRC Trial and 10% vs. 4% for the Dutch Trial), with much of (but not all of) the excess

mortality deriving from associated pancreatic-splenic resection in the D2 groups.[12, 15, 19, 20] Pancreas/spleen-preserving lymph node dissections are now advocated. Particularly since gastric cancer patients tend to be older, with frequent co-morbid conditions, limiting lymphadenectomy to only nodal stations at risk may decrease postoperative mortality by decreasing tissue trauma and decreasing operative time. The Maruyama Program represents a tool to facilitate this.

Only 154 cases had MI < 5, despite the protocol mandate that half the cases be treated with D2 dissection. Median MI for the D2 cases was 10. Fifty-one percent of the D2 cases in the trial had less-than-D2 dissection because of pathology-determined non-compliance with the protocol (i.e. no nodes found in 2 or more node stations which should have been dissected). [11, 12, 21] This may explain why so few of the cases had MI < 5. It must also be emphasized, however, that some "compliant" D2 cases still did not achieve MI < 5; D2 guided surgery "missed" some node stations at risk. Additionally, some D1 cases had MI < 5 either because of favorable characteristics of a particular tumor (e.g. favorable location, depth, size, histology) or because of documented "contamination," with tendency toward "D1.5" dissection.[11, 12, 21]

The management of splenic hilar nodes at station #10 represents a continued challenge for those desiring to plan and execute a "low Maruyama Index" operation. While pancreas-preserving dissection of #11 splenic artery nodes is feasible and recommended, [22, 23] especially when such nodes are at high risk per Maruyama Program, splenic preservation while dissecting splenic hilar nodes is problematic. Splenic resection appears to increase peri-operative mortality and may compromise long-term survival.[11, 15, 20, 24, 25] particularly in the elderly.[26] For this reason, neither splenectomy nor pancreatectomy are recommended, unless required to remove evident actual disease.

This blinded, retrospective analysis of Dutch Trial data suggests that "low Maruyama Index" surgery is associated with significantly increased survival. "Dose-response" with respect to Maruyama Index and survival is also apparent. We advocate using the Maruyama Program, a computerized tool based on actual patient experience, to identify nodal stations at risk, either preoperatively or intra-operatively, in order to customize surgical lymphadenectomy and routinely generate a "low Maruyama Index" operation. Our observations strongly suggest "dumping D " in favor of "low Maruyama Index surgery." Level I, prospective, randomized validation is the next step, and an international trial of this concept is currently being planned.

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