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Anastomotic Leakage after Resection and Bypass for Esophageal Cancer: Lessons Learned from the Past

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A retrospective study of anastomotic leakage has been undertaken in 730 patients who had resection or bypass for carcinoma of the esophagus during the period 1964–1982 at the Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong. Partial or complete gangrene of the substitute loop also resulting in anastomotic disruptions were excluded from this series. Anastomotic leakage due to suture line failure occurred in 182 patients (24.9%).

Two factors were found by multivariate analysis to influence leakage: the type of operation and the choice of organ used as substitute. Leakage occurred more than twice as often in bypass (42.7%) than in resection (18.3%). When the substitute used for reconstruction was viable, jejunum was associated with the lowest incidence of leakage followed by whole stomach, distal stomach, and colon in that order. The risk of leakage for any combination of the type of operation (resection or bypass) and substitute loop used was calculated. The probability of leakage was lowest when a resection was performed and jejunum was used as substitute. In view of the simplicity and relative safety of using the whole stomach, esophagectomy followed by gastric reconstruction is still the procedure of choice for the majority of patients. A bypass procedure using colon as substitute has the highest leakage rate. A low leakage rate should now be obtained, otherwise nonoperative therapy has a legitimate claim as the preferred alternative treatment modality.

Anastomotic leakage is a serious complication of resection or bypass surgery for esophageal carcinoma. Its previous high incidence has been successfully lowered or even eliminated [1–4] by improvements in techniques but, when it does occur, it still has an important influence on outcome and lengthens hospital stay considerably, if not contributing directly to mortality. Leakages have been reported to be more common following bypass procedures than resections [5, 6] and this is also apparent in recent reports [7–9].

This present review of anastomotic leakage during an era of high incidence was conducted in the hope that it might be possible to identify the risk factors and to analyze them. With the low incidence now experienced, differences may not be evident or significant.

The records of 730 patients undergoing resection or bypass for carcinoma of the esophagus at the Department of Surgery, University of Hong Kong, Queen Mary Hospital, Hong Kong, between January, 1964 and June, 1982 have been reviewed and form the basis of this report. The results of surgery, including the occurrence of leakage, have been reported previously in a number of subgroups of this patient population [10–12].

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Material and Methods

During the period under consideration, there were 2,088 patients admitted to our department with the diagnosis of carcinoma of the esophagus. Analysis was performed on the data of 730 patients of this group because they had one-stage resection (531) or bypass (199) and complete data were available (Table 1). The remaining 942 patients who underwent treatment other than one-stage operations are shown in Table 2, which indicates our past management approach.

Of the 730 patients, 598 were male (81.9%) and 132 were female (18.1%) with a mean age of 59 years. The anastomosis under consideration was that between the upper divided esophagus and the organ used for reconstruction or bypass. The diagnosis of leakage at the suture line was made on clinical grounds, usually confirmed by contrast study. Routine postoperative contrast studies to detect subclinical leakages were not carried out.

The 7 factors considered important and therefore selected for analysis were the type of operation, nature of the substitute loop, anastomotic site, route taken by the loop, pathological stage of the tumor, number of layers of suture used, and the use or omission of preoperative nutritional support. These variables were chosen because the type of operation done governed the site of anastomosis and route of substitute, and was related to the stage of the tumor. Different organs used as substitute are known to influence leakage rates and technical and nutritional factors might also be expected to have a determinant role. Records in which any one or more of the 7 factors were absent were rejected. This accounted for the exclusion of 386 patients.

Resection was usually undertaken through the chest and anastomosis was frequently made in the neck. Stomach was most commonly used as a substitute, followed by jejunum and colon. In a bypass procedure, nearly all anastomoses were made in the neck and the route was almost invariably retrosternal or subcutaneous. The choice of substitute for bypass was as for resection. Anastomosis in this series was by the hand-sewn

Table 1. Selection of 730 patients for study.

	n
Total	2,088[a]
One-stage operation	1,146
Incomplete data	386
Gangrene of loop	30
Study group	730
Resection	531
Bypass	199

[a]See Table 2.

Table 2. Treatment in 942 patients who did not have one-stage operation.

Refused treatment	126
Admitted moribund	220
Radiotherapy only	218
Chemotherapy only	18
Staged surgery	117
Laryngectomy included	103
Exploration only	66
Early postoperative death	74

Table 3. Leakage for different procedures in resection and bypass.

Operation	n	Leakage (%)
Resection	531	97 (18.3)
Split-sternum esophagectomy	22	4 (18.2)
Lewis Tanner operation	232	40 (17.2)
Transhiatal esophagectomy	103	16 (15.5)
Esophagogastrectomy	174	37 (21.3)
Bypass	199	85 (42.7)
Kirschner operation	133	60 (45.1)
Other double bypass[a]	9	5 (55.6)
Single bypass	57	20 (35.1)
Total	730	182 (24.9)

[a]Single bypass plus defunctioning of the thoracic esophagus with a Roux loop of jejunum to the abdominal esophagus.

technique: either 1 or 2 layers of interrupted absorbable material. Staplers were not used.

The anastomosis was end of esophagus to gastric fundus when the stomach was used, and end-to-end in the case of jejunum and colon. Nutritional support was administered by gastrostomy feeding and was given on clinical indications.

The 7 variables were analyzed with respect to incidence and outcome of anastomotic failure. In univariate analysis, chi-square statistics were used to compare the proportions of leakage among the groups. In multivariate analysis, logistic regression was used to identify the risk factors influencing leakage. The program used was BMDP-PLR.

Results

A total of 182 (24.9%) leakages occurred in the 730 patients. When the operative procedures were considered, the incidence of leakage in resection and bypass differed markedly. Table 3 shows the different procedures performed for resection and for bypass and their respective leakage rates. In the 199 bypass procedures, leakage occurred in 85 (42.7%), which was more than double the rate in the 531 resections with 97 leakages (18.3%) ($p < 0.001$).

Table 4. Leakage for resection and bypass with respect to site of anastomosis, substitute used, and route of substitute.

	Resection		Bypass	
	n	Leakage (%)	n	Leakage (%)
Site				
Neck	420	79 (18.8)	185	83 (44.9)
Chest	111	18 (16.2)	14	2 (14.3)
Substitute				
Jejunum	96	7 (7.3)	46	12 (26.1)
Whole stomach	324	51 (15.7)	126	57 (45.2)
Distal stomach	87	29 (33.3)	12	6 (50.0)
Colon	24	10 (41.7)	15	10 (66.7)
Route				
Subcutaneous	42	14 (33.3)	136	57 (41.9)
Retrosternal	72	9 (12.5)	49	26 (53.1)
Right chest	267	48 (18.0)	3	1 (33.3)
Left chest	69	14 (20.3)	11	1 (9.1)
Orthotopic	81	12 (14.8)	–	–

Table 4 shows leakage rates for resection and bypass with respect to site of anastomosis, substitute used, and the route of placement of the substitute. The anastomosis was made in the neck in 605 patients (82.9%) and in the chest in 125 (17.1%). In the resections, the site of anastomosis did not influence leakage rate but was significant in the bypass group although the numbers were small. In the 199 patients undergoing bypass, leakage occurred in 83 (44.9%) of 185 neck anastomoses compared with 2 (14.3%) of 14 in the chest. When only substitutes placed in the retrosternal and subcutaneous routes were compared, the leakage rates for resection and bypass were 20.2% (23/114) and 44.9% (83/185), respectively ($p < 0.001$).

The nature of the substitute used in the resections influenced leakage significantly (Table 4). Jejunum had the lowest leakage rate (7.3%) and the highest was for colon (41.7%). Whole stomach, which was used most frequently, had a much better result than distal stomach. The differences between substitutes were not quite so apparent for bypass, but jejunum was still the best in the group.

In the combined group of 730, jejunum (13.4%) had a lower leakage rate than whole stomach (24.0%), but because of the simplicity of its preparation, stomach was used over 3 times more frequently. The differences between the leakage rates of jejunum and whole stomach for resections and bypass were statistically significant. Colon was only used as the loop in 39 instances and the leakage rate was very high in both resection (41.7%) and bypass (66.7%).

The variations in the incidence of leakage among the different routes used for placing the substitute are also shown in Table 4. In resections, the rate was highest when using the subcutaneous route and lowest for the orthotopic and retrosternal routes. For bypass, the right and left chest routes were only used in 14 cases and had low leakage rates; leakages were highest for the subcutaneous and retrosternal routes.

The extent of disease was arbitrarily divided into the 2 categories of confined disease and widespread disease using the following criteria: tumor presence in the resection margins, lymph node involvement, infiltration of adjacent organs, and distant metastases. Leakage rate was not found to be affected by this classification, with 67 (24.6%) occurring in 272 patients

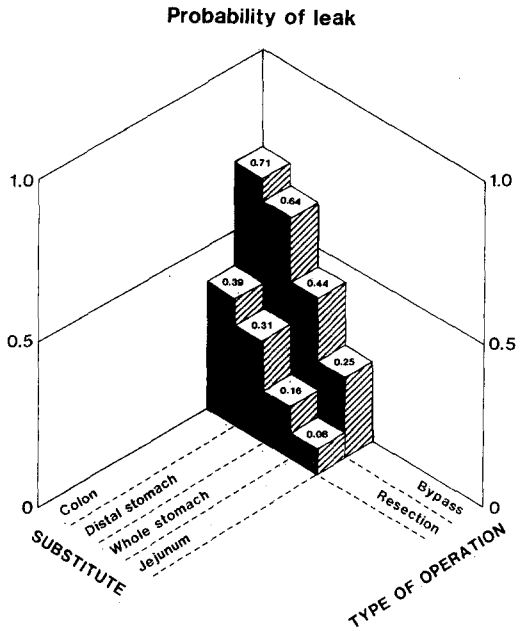

Fig. 1. Probability of leakage for resection and bypass using different substitutes for esophageal replacement.

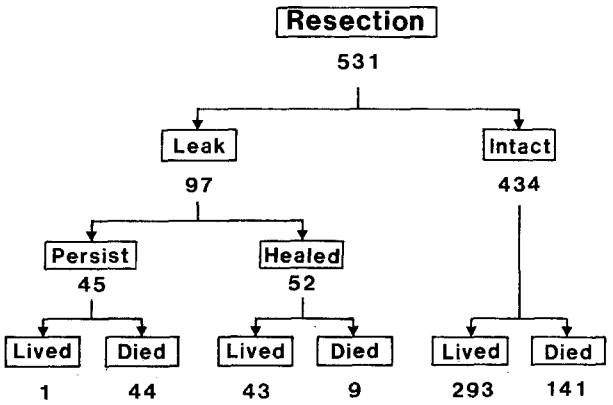

Fig. 2. Outcome of patients who had resection with and without leakage.

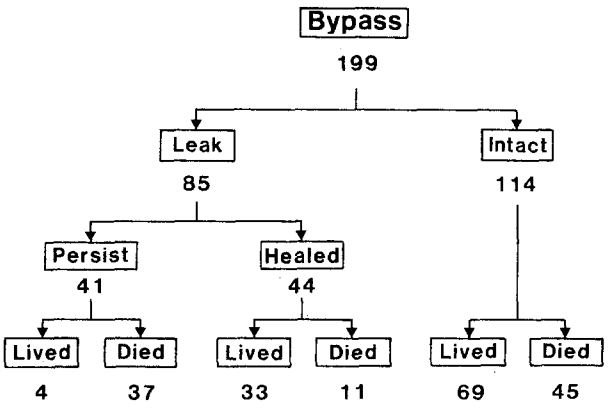

Fig. 3. Outcome of patients who had bypass with and without leakage.

with confined disease, compared with 115 (25.1%) in the 458 patients with widespread disease.

In 587 of the 730 anastomoses, 1 layer of sutures was used and the leakage rate of 24.0% did not differ from that of 28.7% in the 143 where 2 layers were used. Preoperative nutritional support did not influence leakage in the 223 patients (24.7% leakages) given this treatment when compared with the remaining 507 (25.0% leakages) not so treated.

Multivariate analysis showed that only the type of operation and the loop used as substitute influenced leakage. The probability of leakage in each category is represented diagramatically in Fig. 1. The probability of leakage was found to be lowest when resection was performed and jejunum was used for reconstruction, and highest with bypass using a colon loop. The other surgical procedures had leakage rates distributed between these 2 levels, depending on the combination of these 2 independent variables.

The outcome of patients with respect to the presence or absence of leakage and whether the leak healed or persisted for resection and bypass procedures are shown in Figs. 2 and 3. In summary, healing took place in 53.6% (52/97) of patients with resection and the mortality of the group was 17.3% (9/52). Those whose leakage persisted had a mortality of 97.8% (44/45). For bypass, the corresponding figures were 51.8% (44/85), 25% (11/44), and 90.2% (37/41). The differences between resection and bypass were not statistically significant. When a leak did not heal, the mortality was almost absolute.

When leakage developed, the overall hospital mortality was 54.6% (53/97) for resection, which was very similar to the 56.5% (48/85) for bypass. As expected, the absence of leakage conferred a lower hospital mortality for both resection (32.5%) and bypass (39.5%). For the total group (resection and bypass), leakage was associated with a hospital mortality of 55.5% compared with 33.9% for an intact anastomosis ($p < 0.001$). The overall hospital mortality for the series was 39.3% (287/730).

The mortality rates of anastomotic leakage in the neck and chest were 53.2% (42/79) and 61.1% (11/18) following resections, a difference which is not significant. This indicates that when a leakage occurred, it was equally lethal in both the neck and chest.

The 386 patients excluded owing to incomplete data were further analyzed. The most common reason for exclusion (319/386) was failure to record the number of suture layers used. This factor was not shown to influence leakage rate in the study. The incidence and distribution of leakage among the various operation types did not differ from the results in the 730 patients in the study group, and hospital mortality rates for leaked and intact anastomoses were also similar to the study group.

Using mathematical modeling, it was found that the accuracy in predicting leakage for the 730 patients (from which the model was derived) was 66.6% (Table 5). When the same model was applied to the 368 patients previously excluded because 1 or more of the 7 factors were absent, the accuracy was 57.3%. Eighteen of the 386 patients (Table 1) had 1 or both values of the 2 independent variables missing and so were further excluded.

Discussion

Leakage of the anastomosis defeats the primary objective of esophageal cancer surgery because the patient cannot eat and the mortality associated with the leakage is very high. Unless a

Table 5. Accuracy of mathematical model in predicting anastomotic leakage.

	Present series (n = 730)	Retrospective series (n = 368)
Sensitivity (%)	66.1	56.4
Specificity (%)	68.1	60.0
Predictive value for leak (%)	40.0	32.4
Predictive value for no leak (%)	86.2	80.2
Accuracy (%)	66.6	57.3

low leakage rate can be obtained following surgery, other forms of treatment might be preferable.

In our earlier experience, the incidence of leakage was high by present standards but was comparable to the leakage rate then current. Because of the large number of patients in our series together with a substantial leakage rate at that time, we thought it would be instructive to analyze the data to identify the important risk factors and also to establish a database for comparison with our more recent results. Since this study is a retrospective one, only qualified conclusions can be drawn. A high leakage rate for esophageal anastomosis has been blamed on the intrinsic structure of the esophagus [13] and the depleted nutritional state in patients with dysphagia [14]. While these features may contribute to a high leakage rate generally, our data would indicate that the type of operation, (which is dictated by the stage of disease), and the choice of esophageal substitute are of more overriding importance. By selection, it is possible to resect only patients with early stage disease and in good physiological condition, thus reducing the leakage rate [15]. But by applying this approach, many patients would be denied the benefits of successful surgery.

The 3 interrelating factors in reconstruction (after resection or for bypass) are the site of anastomosis, the substitute used, and the route for its placement. These are, in turn, determined by the level of the tumor, the extent of local tumor invasion and, when present, the pattern of metastatic spread. The choice of operation is, thus, constrained by the pathological features of the primary tumor, the target organs of secondaries, the patient's cardiopulmonary status, as well as by the surgeon's experience and preference.

The main factor that determines leakage, established in this study, was the type of operation. Resection was associated with a leakage rate that was less than half that of bypass. In a bypass operation, the stage of the disease was very advanced and the anastomosis was almost always performed in the neck. When comparing only neck anastomosis for resection and bypass, leakage rate for bypass was still much higher (44.9% versus 18.8%). Furthermore, when only the subcutaneous and retrosternal routes were selected for comparison between the 2 operations, the differential in leakage rates was maintained. Therefore, the stage of disease and, thus, the type of operations had a critical effect on the incidence of leakage. The reasons for this influence remain speculative.

The second independent factor was the identity of the substitute. Jejunum as a substitute had the lowest leakage rate, but it was also the most difficult to prepare especially when a long loop was required to reach the neck. Occasionally, the anatomy of the jejunal vasculature rendered it unsuitable and the incidence of gangrene for a jejunal loop was also much higher than the stomach. These factors mitigate against its more regular usage.

Stomach was, thus, the first choice for reconstruction and when the whole stomach was available for substitution, good results were obtained. That only 1 anastomosis was required added much to its appeal [16, 17].

Use of the distal stomach (after an esophagogastrectomy), unlike the whole stomach, was associated with a high leakage rate. This might have been due to difficulties encountered in performing a technically satisfactory anastomosis between the esophagus and the tip of the stomach tube (with a T-junction), or through the anterior or posterior wall of the distal stomach when the area available for anastomosis was already limited. Furthermore, if the line of gastric closure was inverted, the stomach tube might become bulky and the technical difficulties enhanced. Probably for these reasons, this type of anastomosis has a higher leakage rate [18].

Colon has traditionally been a substitute associated with frequent anastomotic failures [19, 20] and our findings confirmed this. Explanations such as an apparently poor blood supply as well as the presence of a highly infective bacterial flora when bowel preparation had not been ideal are difficult to validate. Improved technique had led to favorable results [21, 22] and our low leakage rate now obtained would support this contention.

For an anastomosis to be made in the neck, a longer substitute loop is required than for one made in the chest. In addition, for all neck anastomoses, the length of the loop is greater when placed in the subcutaneous or retrosternal position than when placed orthotopically [23]. Furthermore, the angulations which the loop in the subcutaneous position undergo before reaching the cervical esophagus for anastomosis may also contribute to jeopardize its blood supply and, in this respect, the colon is particularly vulnerable. The technical and physical features of preparing a long loop and placing it in the subcutaneous route may, therefore, explain why a high leakage was found in this type of reconstruction. For bypass operations, as the anastomosis was nearly always in the neck, this, coupled with the advanced stage of the disease and the factors cited above, aggregate to produce the extremely high leakage rate noted.

Once leakages had developed, only half of them eventually healed. Predictably, those patients with healed anastomoses had a much improved chance of survival. Those not healed virtually all died in the hospital as a direct result of this complication.

One of the justifications cited for performing a neck rather than a chest anastomosis was that a leak in the neck was less lethal than one in the chest. Our data do not support this belief. A leak at either site was equally catastrophic with respect to outcome, and, conversely, leakages in the chest had as much likelihood of healing as those in the neck.

The lack of precision in predicting the development of leakage (or otherwise) using a mathematical model, derived from and applied to the series of patients who provided the data for modeling (as well as when it was used on a retrospective group) indicates that other factors in addition to the 2 identified independent variables were relevant. A prime candidate for such additional factor is surgical technique. The influence of surgical technique had not been and could not be easily evaluated although its importance has always been admitted but

seldom quantified. Recent publications emphasizing the significance of technical craft to surgical outcome are most timely [24, 25].

Leakage of anastomoses at our institution in the last few years has been reduced to 5.3% for resection and 15.7% for bypass. The use of the stapler, which had been found by a number of surgeons to produce a safe esophageal anastomosis, was shown by us not to be superior to a hand-sewn technique [4]. A 1-layer continuous suture using a monofilament absorbable synthetic material appears, for the present, to be optimal. Although a similarly significant reduction in the leakage rate for bypass has also now been achieved, the relative difference between leakage rates for resection and bypass remains unchanged.

From this study, we have documented the incidence of leakage in the past to be high and identified the important influence of the type of operation and the substitute used on leakage. Whatever the leakage rate, the risk to life remains substantial when this complication occurred. Our study confirmed, in retrospect, that a subtotal esophageal resection through the right chest followed by the use of the whole stomach for anastomosis in the thoracic cavity is an operation that is technically straight-forward, biologically adequate, and associated with one of the lowest risks of leakage when compared with other procedures [26]. By contrast, the use of a colon loop for bypass to the neck in the subcutaneous position is associated with the highest risk and the value of such a procedure should be reconsidered. Knowledge of these relative risks should enable us to consider alternative treatments when the possibility of anastomotic leakage, and, therefore, mortality, in specific circumstances is high. Conversely, the known safety of certain procedures should encourage us to employ them more widely and confidently in patients for whom such procedures are sound options.

Résumé

Une étude rétrospective a été entreprise chez 730 patients ayant eu une résection ou un bypass pour cancer de l'oesophage au cours des années 1964–1982 dans le département de chirurgie de l'Hôpital Universtaire Queen Mary à Hong Kong. Les fuites anastomotiques dues à une ischémie avec grangrène complète ou partielle de l'organe de remplacement ont été exclues. Cent quatre-vingt deux patients (24.9%) présentaient une déhiscence au niveau de la suture.

A l'analyse multifactorielle, deux facteurs ont été incriminés dans ces déhiscences: le type de l'opération et le choix de l'organe utilisé pour le remplacement. Les fuites anastomotiques étaient deux fois plus fréquentes lorsqu'il s'agissait d'un bypass (42.7%) que quand il s'agissait d'une résection (18.3%). Outre les problèmes ischémiques, la fréquence des fuites était inférieure lorsque'on utilisait le jéjunum. Venaient ensuite dans l'ordre l'estomac entier, l'estomac distal et le côlon. En combinant le type de l'intervention et l'organe utilisé, on obtenait un risque minimum de fuite anastomotique dans la résection associée à une anse jéjunale montée. Mais comme il est plus simple d'utiliser l'estomac entier, on préfère ce procédé pour la plupart des patients. Le bypass utilisant le côlon présentait le plus grand taux de fuite anastomotique. Il faut s'efforcer d'obtenir un taux de déhiscence anastomotique bas: autrement on doit préférer un traitement non chirurgical des cancers de l'oesophage.

Resumen

Se realizó un estudio retrospectivo de las fugas anastomóticas en 730 pacientes que fueron sometidos a resección o a derivación por carcinoma de esófago en el período 1964–1982 en el Departamento de Cirugía de la Universidad de Hong Kong del Queen Mary Hospital, Hong Kong. Las gangrenas parcial o completas del asa sustituta que también hubieran dado lugar a dehiscencias anastomóticas fueron excluídas de la serie. La fuga anastomótica debida a falla de la línea de sutura se presentó en 182 pacientes (24.9%).

Dos factores fueron identificados mediante el análisis multivariable como de influencia en la fuga anastomótica: el tipo de operación y el órgano escogido como sustituto. La fuga se presentó con una frecuencia mayor del doble en las operaciones de derivación (42.7%) que en las resecciones (18.3%). Cuando el sustituto utilizado para la reconstrucción se mantuvo viable, el yeyuno apareció asociado con la más baja incidencia, seguido del estómago total, del estómago distal, y del colon, en este orden. El riesgo de fuga para cualquier combinación de operación (resección o derivación) con el asa sustituta utilizada, fue calculado. La probabilidad de fuga fue menor para la combinación de resección con el yeyuno como sustituto. Sin embargo, en vista de la simplicidad y seguridad relativa de utilizar la totalidad del estómago, la esofaguectomía con reconstrucción gástrica es todavía el procedimiento de elección para la mayoría de los pacientes. La derivación utilizando el colon como sustituto posee la más alta tasa de fuga anastomótica. Una baja tasa debe ser lograda en la actualidad, o de lo contrario la terapia no operatoria puede tener justificación como la modalidad terapéutica de preferencia.

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Invited Commentary

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This is a particularly instructive article that comes from a team that most likely has the largest experience with esophageal surgery in the world. Based on the results of their study, the authors conclude that: (a) resections are associated with less anastomotic leakage than bypass surgery, (b) jejunum substitute was associated with less anastomotic leakage than stomach or colon. The second conclusion is very surprising for us in the Western part of the world because, in Europe at least, the jejunum does not always easily reach the upper thoracic or cervical esophagus. This seems to be true even for the authors because, in spite of what they found in their study, they prefer to use the whole stomach rather than the jejunum for reconstruction after esophagectomy.

It is unfortunate and dismaying to us, however, that one-third of the patients were lost to analysis because of incomplete data, or elimination. Incomplete data is, indeed, one major drawback of long retrospective studies. As well, the fact that 30 furthe patients with gangrene of their loop were withheld from analysi might bias statistics in favor of jejunum transplants. Moreover one would like to know why the 74 patients who died in th early postoperative period were not included, and what was th cause of death. All this interferes with the mode of selection o patients and can lead to contradictory results.

Another question that comes to mind is the definition o judgment criteria. The model used by the authors is most likel satisfactory because the predictive value for anastomotic leak was 40% whereas the overall prevalence is 30% and th prevalence in bypasses is 42.7%. This might mean, however that the authors did not choose appropriate end-points sinc they did not increase (or very slightly so) the a priori probabilit (prevalence) of anastomotic leak.

Undoubtedly, this article would have more weight if th following predictive factors had been studied: (a) nutritiona status before operation (and not whether nutritional suppor was used) (b) tumor stage, and (c) the site of the tumor and therefore, most importantly, the site of anastomosis and th results according to the type of substitute for each site.

Once again, as a European, and even though the techniqu was invented in Switzerland, it is very difficult to believe tha the best substitute for esophageal replacement with anastomc sis performed in the neck is a Roux-en-Y jejunal transplant.