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Editorial Update

Improved Prognosis of Resected Esophageal Cancer

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Abstract. Because of the perceived high risk of esophagectomy and the assumed poor long-term results, the role of surgical resection as the mainstay of treatment for localized esophageal cancer is currently being challenged. Early tumors are increasingly approached by endoscopic mucosectomy or mucosal ablation techniques, whereas combined radiochemotherapy without surgery has become the treatment of choice for locally advanced tumors at many institutions. Several recent reports and our experience, however, indicate that surgical resection of esophageal cancer has become a safe procedure and long-term survival rates after surgical resection have improved markedly during the past two decades. A number of factors have been associated with the marked reduction in postoperative mortality and improved long-term survival after surgical resection. They include changes in the epidemiology with an increased rate of adenocarcinoma mostly located distally, patient selection for surgery, improvements in surgical technique and perioperative management, and the use of neoadjuvant treatment protocols. The treatment strategy and extent of the surgical procedure can now be tailored based on histologic tumor type, tumor location, tumor stage, and the general condition of the patient. With an individualized approach, surgical resection of esophageal cancer can predictably offer cure. Surgical resection thus remains the major pillar in the successful treatment of esophageal cancer.

The therapeutic approach to esophageal cancer has changed dramatically during the last 20 years. In the past, surgical resection was the only reasonable treatment for the usually advanced esophageal cancer. Palliation of dysphagia was the major goal, cure was considered a chance phenomenon [1, 2]. Postoperative mortality rates were high, but they were accepted because there were no reasonable treatment alternatives. After the introduction of effective endoluminal treatment modalities (e.g., stents) and percutaneous radiochemotherapy for locally advanced tumors, the focus of surgery changed from palliation to cure [3, 4]. Because of the perceived high risk of esophagectomy and the poor long-term results, the role of surgical resection in the curative approach to esophageal cancer is, however, currently being challenged. Early tumors are increasingly approached by endoscopic mucosectomy or mucosal ablation techniques [5], and combined radiochemotherapy without surgery has become the treatment of choice for locally advanced tumors at many institutions [6].

Although in many areas around the world the long-term prognosis of patients with a resected esophageal cancer remains dismal, 5-year survival rates in excess of 40% are now consistently reported from numerous centers in subgroups of patients [3, 4]. Recently, several reports also showed favorable trends in postoperative mortality and long-term survival of large, apparently unselected patient populations who underwent esophagectomy for esophageal cancer [7–10].

In an analysis from Hong Kong, Law et al. reported an improved median survival time; it increased from 15.8 months in patients undergoing esophagectomy during 1990–1995 to 25.6 months in patients who had undergone resection during 1995–2000. The postoperative mortality was 0% during the latter time period [7].

A recent report from the United States showed an increase in the median survival time after resection of esophageal cancer from 17 months to 34 months and a reduction of the postoperative mortality from 12% to 6% during the past 30 years [8].

In a large consecutive series of resected squamous cell esophageal cancers from Japan, the date of surgery was also identified as an independent prognostic factor for locally advanced tumors. The 5-year survival in patients with stage IIa–IV disease operated on before 1995 was 17.7%, but it improved to 37.6% in patients with similarly advanced tumor stages operated on after 1995. Hospital mortality decreased from 11.7% during the first period to 5.4% during the second period [9].

These observations match our experience with almost 1300 esophagectomies for esophageal cancer during the past 20 years. As shown in Figure 1, there was a marked improvement in long-term survival during three consecutive time periods. The postoperative 30-day mortality dropped from around 10% before 1990 to consistently below 2% since 1994 (Fig. 2).

Factors Associated with Improved Prognosis after Esophagectomy for Esophageal Cancer

Because most of the studies reporting improved survival after esophagectomy over time are retrospective in nature, with multiple possible interfering factors, a clear reason for this development is difficult to determine. In all of the reports, the improved prognosis was associated with an increased rate of complete tumor resections (R0 resections) [7–10]. Some studies also noted an effect of tumor "down-staging" to more favorable categories by applying neoadju-

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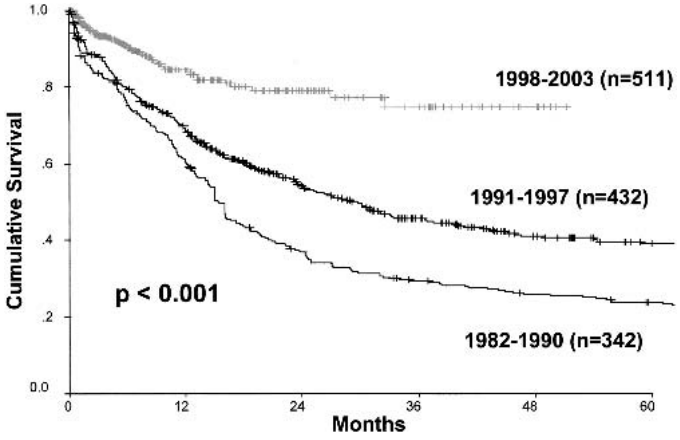

Fig. 1. Long-term prognosis of patients with resected esophageal cancer for three consecutive time periods. (Data of the Chirurgische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Germany.)

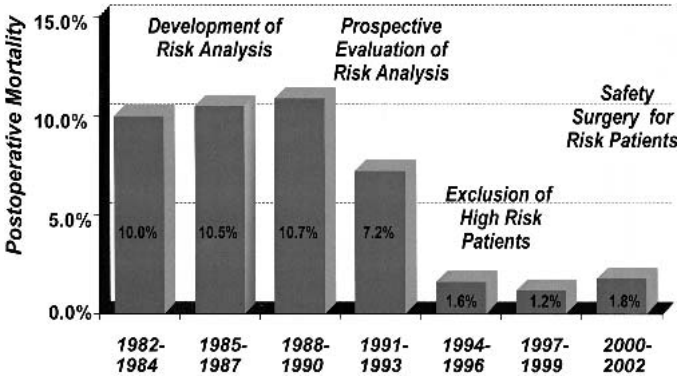

Fig. 2. Decreasing postoperative mortality after esophagectomy for esophageal cancer over consecutive time periods. (Data of the Chirurgische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Germany.)

vant treatment protocols. Although some of the improved prognosis after esophagectomy may be due to a selection bias, the overall trend toward a better prognosis is thus most likely multifactorial in nature. It appears to be at least in part related to changing epidemiology and early detection, improved staging modalities, advances in surgical technique and perioperative management, and increased use of preoperative neoadjuvant treatment protocols.

Changing Epidemiology

In the Western hemisphere, there has been a striking increase in the prevalence of adenocarcinoma and a shift from upper gastrointestinal cancers to a predominantly distal esophageal and gastroesophageal junction location [3, 4, 11, 12]. At many institutions in Europe and North America, esophageal adenocarcinomas now clearly outnumber squamous cell esophageal cancers.

The histologic tumor type has been identified as an independent prognostic factor after esophagectomy [11]. In a recent multivariate analysis of almost 1300 patients with resected esophageal cancer we confirmed that, irrespective of other possibly confounding factors, the prognosis of patients with a resected esophageal adeno-

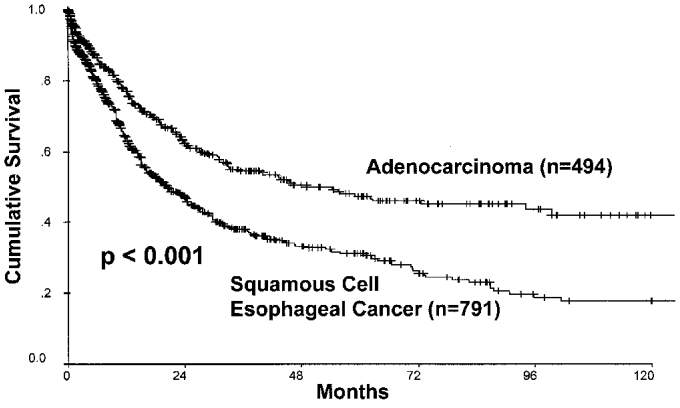

Fig. 3. Overall prognosis of resected esophageal adenocarcinoma and squamous cell cancer. (Data of the Chirurgische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Germany.)

carcinoma is markedly better than that of patients with a resected squamous cell cancer (Fig. 3). This difference is highly significant despite the fact that at the time of presentation patients with adenocarcinoma are on average 8 to 10 years older than those with squamous cell esophageal cancer. A better prognosis for patients with a resected adenocarcinoma has also been reported by Orringer et al. [13]. The reason for this observation is unclear, but it may be related to a different biologic behavior, later onset and different pattern of lymphatic spread, lesser degree and prevalence of lymphatic vessel invasion (lymphangiosis carcinomatosus), a more favorable physiologic risk profile for extended surgery, and a lower likelihood of patients with esophageal adenocarcinoma to develop postoperative complications [11, 14]. Consequently, it has now become clear that adenocarcinoma and squamous cell cancer of the esophagus must be considered entirely different tumor entities [4].

In patients with squamous cell esophageal cancer, a tumor location in the distal esophagus has been associated with a better prognosis. Law et al. associated an increasing prevalence of distal esophageal squamous cell cancer with the observed overall improvement of resected esophageal cancer during the past years [7]. Worse survival rates for cancer of the upper esophagus have also been reported by several other authors [4]. The poor prognosis of supracarinal tumors is attributed to the fact that radical resection of tumors above the level of the tracheal bifurcation is compromised by the proximity of the trachea and recurrent laryngeal nerves as well as the extensive oral and aboral lymphatic spread of such tumors, which makes tumor clearance more demanding.

The increased prevalence of more distal tumor locations and the rapid rise in the prevalence of adenocarcinoma may thus have contributed in part to the better overall prognosis for patients with a resected esophageal cancer.

Increased Rate of Diagnosing Early Tumors

Early diagnosis is one of the pillars of cure in patients with malignant tumors. Except in a few geographic high risk areas, the goal of early diagnosis has been difficult to achieve with squamous cell esophageal cancers. This situation is different for esophageal adenocarcinoma. Because the predisposing condition (severe, long-lasting gastroesophageal reflux disease) and the precursor lesion (Barrett's esophagus) are well known, esophageal adenocarcinomas are increasingly diagnosed at early stages by endoscopic sur-

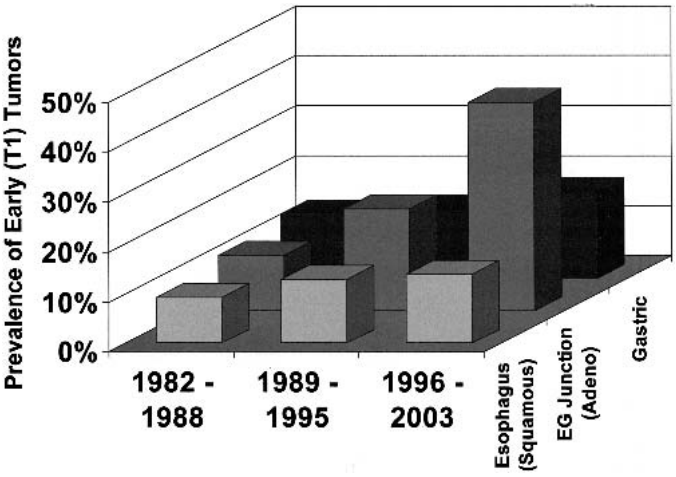

Fig. 4. Prevalence of early tumors among patients with resected upper gastrointestinal cancer over consecutive time periods. EG: esophagogastric. (Data of the Chirurgische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Germany.)

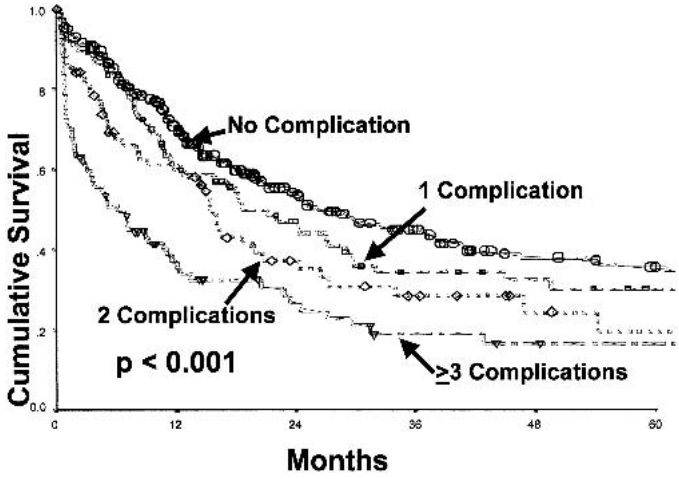

Fig. 5. Overall prognosis of resected esophageal carcinoma in relation to the number of postoperative complications. (Data of the Chirurgische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Germany.)

veillance programs of the populations at risk [15]. Although the cost–benefit aspects of endoscopic surveillance in patients with known Barrett's esophagus and long-lasting reflux disease are still controversial, it is clear that tumors detected by a surveillance program are usually at an earlier stage and the patients have significantly better survival than those with tumors detected in a nonsurveillance manner [16].

In our experience, the rate of early adenocarcinoma has risen dramatically during the past decade owing to the liberal inclusion of patients with Barrett's esophagus in endoscopic surveillance programs in Germany [17]. Whereas early tumors were uncommon among the surgically treated patients with esophageal adenocarcinoma before 1990, early Barrett's carcinoma now constitutes about 40% of all resected esophageal adenocarcinomas (Fig. 4). In contrast to Japanese series, the incidence of finding early gastric cancer and early squamous cell cancer of the esophagus has not changed significantly at our institution during the same time period. Although the increased prevalence of early esophageal adenocarcinoma may in part have contributed to the overall improved prognosis for patients with resected esophageal cancer, it cannot explain the increased survival rate of patients with squamous cell esophageal cancer and those with locally advanced adenocarcinoma, which still account for the majority of patients undergoing esophagectomy.

Improvements in Preoperative Staging, Patient Selection for Surgical Resection, Operative Technique and Perioperative Management

The major goals of the preoperative evaluation of patients with esophageal cancer are to exclude distant metastases, decide whether a complete macroscopic and microscopic tumor resection of the primary tumor and its lymphatic drainage (R0 resection) can be achieved, and assess whether the patient can tolerate an extensive surgical procedure [18]. Some of the tools to achieve these goals have markedly improved during the past decade.

In the past, percutaneous ultrasonography, plain chest radiography, and computed tomography (CT) scanning have been routinely employed to determine if distant metastases are present. Today these techniques are increasingly being replaced by the more accurate positron emission tomography (PET) and, in patients with locally advanced adenocarcinoma of the distal esophagus, diagnostic laparoscopy. In our and others' experience, the diagnostic gain of these new technologies (i.e., relevant new information not available by standard imaging modalities) is approximately 20% [18].

The T category and relation to the surrounding structures of the primary tumor are the essential factors for predicting R0 resectability. In the past, contrast radiography was the only means (and an indirect one at that) to assess resectability. This situation has markedly improved with the introduction of endoscopic ultrasonography and high resolution multislice CT scanning [18].

In our experience, a systematic risk analysis with a dedicated composite scoring system [19] has proved essential to assess the physiologic status and identify patients with a high postoperative mortality risk. Strict application of this detailed organ function scoring system, the consequent improvement of compromised organ function prior to surgery, and a two-stage surgical safety concept in high risk situations [20] were closely related to maintaining a postoperative mortality rate after esophagectomy consistently below 2% in recent years [19] (Fig. 2). This is in concert with other studies that have related a reduction in postoperative mortality to more stringent patient selection.

Simultaneous with these developments, surgical techniques and perioperative management have been refined at many centers in recent years. Standardization of resection techniques, peridural anesthesia, early extubation, and aggressive pre- and postoperative physical therapy are only some of the factors that have been adopted as routine in the past few years [4].

The individual or combined contribution of these factors to improved long-term survival probably is substantial but difficult to quantitate from the available data. Possible surrogate markers of these developments (e.g., number of perioperative blood transfusions required, postoperative morbidity), however, have been repeatedly identified as independent prognostic factors after esophagectomy (Fig. 5) [21].

Current data convincingly indicate that only hospitals with a sufficient case load of esophageal cancer patients ("hospital volume") and a dedicated interest in the management of this disease ("centers of excellence") can provide the required expertise for patient

evaluation, selection for surgical resection, safe resection and reconstruction, and a smooth postoperative course. The case load, or "volume," not only is the most critical factor for postoperative mortality, it also appears to be a predictor of long-term survival in patients with esophageal cancer [22, 23].

Lymphadenectomy

The lymph node status and the number of positive lymph nodes represent the major independent prognostic factors in patients with complete tumor resection [21]. Although this argues for extended resection, no clear overall survival benefit has so far been demonstrated for extended lymphadenectomy in patients with squamous cell cancer or adenocarcinoma of the esophagus in the Western world. Several studies, however, indicate that extended lymphadenectomy may improve survival in the subgroup of patients who have a limited number of positive lymph nodes or early stages of lymphatic spread (i.e., lymph node microinvolvement) [24]. The so-called lymph node ratio (i.e., the ratio between positive and removed nodes) constitutes a parameter for estimating the extent of lymph node dissection in relation to lymphatic tumor spread. A lymph node ratio of < 0.2 is an independent prognostic factor for patients with squamous cell cancer and adenocarcinoma of the esophagus [21]. In the series reported by Ando et al., the improved prognosis for patients who had undergone resection for esophageal cancer during the more recent time period was significantly related to a higher number of removed lymph nodes [9]; i.e., a lower lymph node ratio.

Despite enthusiasm for extended lymphadenectomy in Japan, this concept has not been widely adopted in the Western world because of the increased postoperative morbidity associated with it [24]. Rather, patients with locally advanced tumors and tumors located at or above the level of the tracheal bifurcation, who may theoretically benefit from three-field lymph node dissection, are usually subjected to multimodal therapeutic concepts with neoadjuvant or primary combined radiochemotherapy. Some recent series, however, have confirmed that extended lymph node dissection can also be performed in experienced centers in the Western world with low mortality and reasonable morbidity [25, 26]. This approach has resulted in impressive long-term survival rates similar to those reported in Japanese series. Even if the evidence is not yet decisive, these observations suggest that systematic lymph node dissection can contribute to improved prognosis of resected esophageal carcinoma. Nevertheless, randomized trials without selection bias are essential to confirm the benefit of extended lymphadenectomy.

Multimodal Therapy

Preoperative chemotherapy or combined radiochemotherapy in patients with esophageal cancer was introduced more than 20 years ago with the primary goal of inducing a down-staging of locally advanced tumors, thereby improving the chance for complete tumor resection during subsequent surgery. Although it is clear today that neoadjuvant therapy can induce marked tumor regression and even complete remission in a subgroup of patients, there has been no consistent survival advantage with this approach over surgical resection alone in most prospective controlled trials [27, 28]. Only two of the numerous randomized trials have shown a survival benefit with combined preoperative radiochemotherapy [29] or preoperative chemotherapy [30] over resection alone. Nevertheless, in our and others' experience, the improved prognosis associated with resected esophageal cancer during more recent time intervals was significantly associated with an increased use of neoadjuvant treatment protocols [7, 8] (Fig. 6). The use of neoadjuvant therapy was the most significant multivariate factor associated with the ability to achieve a complete R0 resection in these studies. In our practice, neoadjuvant chemotherapy (for esophageal adenocarcinoma) or combined neoadjuvant radiochemotherapy (for squamous cell esophageal cancer) has been employed increasingly during the past 20 years (Fig. 6) and now constitutes the standard of care for all patients with locally advanced tumors, who do not have contraindications for this approach [27].

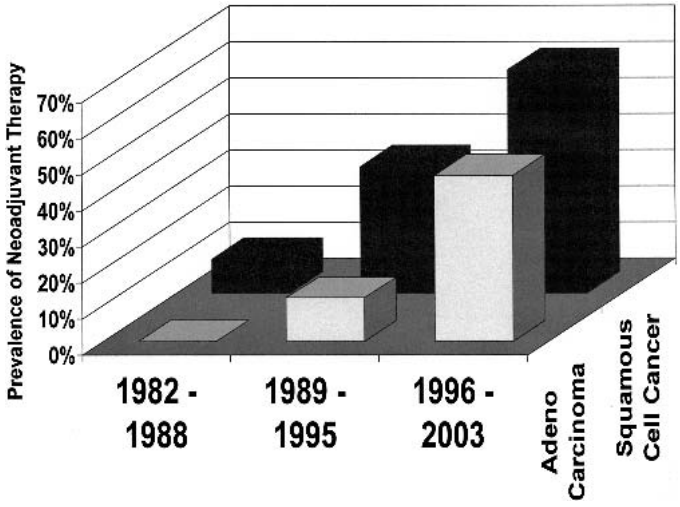

Fig. 6. Prevalence of patients receiving neoadjuvant therapy prior to esophageal resection over consecutive time periods. (Data of the Chirurgische Klinik und Poliklinik, Klinikum rechts der Isar, Technische Universität München, Germany.)

Despite the overall disappointing results of most randomized trials on neoadjuvant therapy for esophageal cancer, there appears to be an impact on the eventual outcome of resection in those who respond to neoadjuvant treatment. Because only about 40% to 60% of patients do respond to neoadjuvant treatment, the current focus of research is to identify these "responders" early during the neoadjuvant treatment and search for molecular markers that would allow us to predict a response before initiating preoperative therapy [27]. A decrease in the glucose uptake of the primary tumor on fluorodeoxyglucose (FDG)-PET scanning 2 weeks after initiation of neoadjuvant therapy has shown promising results as a tool for early "response" evaluation [31]. A set of molecular parameters for response prediction is currently being established using the new microarray technology.

Minimally Invasive Approaches and Limited Extent of Surgical Resection

The still substantial morbidity and poor postoperative quality of life associated with extended esophagectomy has stimulated efforts to search for less invasive, more limited approaches to esophageal cancer. Minimally invasive surgery has been introduced to reduce the access-induced trauma of extended esophagectomy. Large series on laparoscopic and thoracoscopic esophagectomies have been

reported [32, 33] and have clearly shown the feasibility of a minimally invasive approach to esophageal cancer. The benefits, however, are still discussed controversially because the minimally invasive approach to esophageal cancer is more complex than it is to most other gastrointestinal malignancies. In addition, there are still concerns regarding the adequacy of tumor and lymph node clearance. In most series, postoperative morbidity and mortality rates have not been substantially reduced by the minimally invasive approach, and there are still no long-term data assessing the prognostic impact.

Because of the virtual absence of lymph node metastases in patients with early distal esophageal adenocarcinoma, limited surgical and endoscopic resection have been evaluated in such patients [5]. We have assessed limited transabdominal resection of the distal esophagus and gastroesophageal junction with regional lymphadenectomy [17]. To avoid postoperative reflux, reconstruction is performed by interposing a pedicled jejunal segment. In our experience with more than 60 such procedures, complete tumor resection (R0) resection was achieved in all instances. At a median follow-up of 43 months, there have been no recurrences or deaths. Quality of life assessment showed no evidence of gastroesophageal reflux and good to excellent swallowing function in more than 90% of the patients. Similar encouraging data with limited resection in patients with early tumors have also been reported from several other centers, particularly when the vagus nerve can be preserved during the resection [34].

The new technology of endoscopic mucosal resection offers an even more limited approach to early esophageal cancer [5]. Because lymphadenectomy is not possible with this technique, endoscopic mucosal resection can be recommended only in patients with a low likelihood of lymphatic spread (i.e., high grade neoplasia or pT1a tumors). The frequent multicentric tumor growth, the inaccuracy of current preoperative staging modalities for differentiating mucosal from submucosal tumors, and the persistence of precancerous lesions (e.g., Barrett's esophagus) with a high rate of tumor recurrences, however, currently limit the broad clinical application of this truly limited procedure.

The impact of limited resection and minimally invasive approaches on the overall prognosis of patients with esophageal cancer is, by nature of the underlying disease, small. In terms of improved quality of life, reduced access morbidity, and preservation of the healthy organ, these new approaches, however, have the potential to replace the more radical surgical strategies in selected subgroups of patients.

Outlook: Individualized Therapy

The improvements in the overall survival of patients with esophageal cancer during the past few years have been achieved by more stringent patient selection, improved surgical techniques and perioperative management, and tailored therapeutic strategies. The latter are currently based on the histologic tumor type, tumor location, tumor stage at the time of presentation, and the physiologic status of the patient. With these improvements, cure has become possible in a large proportion of patients undergoing esophagectomy for esophageal cancer. Substantial further advances can now be expected only by refining the individualization of the treatment strategies. Tailoring the extent of resection to the radicality required for cure and targeting pre- and postoperative treatment to the individual situation are the goals. To achieve these goals, we must widen our horizon beyond the scope of traditional surgical concepts and embrace new technology.

The perceived need to perform extended lymphadenectomy in all patients with resectable esophageal cancer is today the major cause of postoperative morbidity. More selective use and tailored extent of lymphadenectomy in those who may benefit from it is desirable. Despite advancements, it is currently still difficult to predict reliably the presence and extent of lymph node metastases in an individual patient based on noninvasive imaging modalities. Identification of the sentinel node, which permits detection of the first draining node from a primary lesion, has been used successfully to individualize lymph node dissection for melanoma and breast cancer and has also been investigated in patients with esophageal cancer [35, 36]. The first reports are encouraging. Provided these data are confirmed, sentinel node mapping may be the key to individualized, tailored lymphadenectomy concepts in patients with esophageal cancer. Reliable pretherapeutic identification of patients with early tumors who do not have lymph node metastases will also set the stage for wider use of more limited, organ-preserving approaches.

Another exciting new avenue for individualization of treatment is the targeted use of neoadjuvant and adjuvant treatment modalities based on gene expression profiles and sensitivity testing. With current global approaches, 50% or more of the patients who undergo neoadjuvant or adjuvant therapy are subjected to the associated morbidity but do not receive a benefit because they do not respond. FDG-PET scanning has been shown to be a useful tool for identifying such nonresponders early after the onset of such therapies. New molecular techniques based on DNA microarray analysis of tumor biopsies hold promise for identifying a set of biologic factors that predict response to individual substances or treatment modalities and allow chemo- and radiosensitivity testing of each tumor before neoadjuvant or adjuvant therapy is begun. If these promises hold true, molecular sensitivity testing and response prediction will become a major area for truly individualized treatment strategies in patients with esophageal cancer [37].

Résumé. En raison d'un haut risque opératoire associé à l'oesophagectomie, et les mauvais résultats à distance de la résection chirurgicale, le rôle de la résection chirurgicale comme traitement standard pour cancer de l'oesophage localisé est à présent discutable. La mucosectomie endoscopique, ou les techniques d'ablation mucosale combinée à la radiochimiothérapie sans chirurgie sont devenus le traitement de choix dans beaucoup d'institutions pour les tumeurs localisées. A la lumière de plusieurs rapports récents et en accord avec l'expérience des auteurs, cependant, la résection chirurgicale est devenue un procédé sure et la survie à distance après résection chirurgicale s'est améliorée énormément pendant les deux dernières décennies. Un certain nombre de facteurs sont associés à la réduction de la mortalité postopératoire et l'amélioration de la survie à long terme après résection chirurgicale. Ces facteurs sont les changements épidémiologiques avec une augmentation de la proportion d'adénocarcinome surtout dans l'oesophage distal, une meilleure sélection des patients pour la chirurgie, des améliorations de la technique chirurgicale et de la prise en charge périopératoire ainsi que l'utilisation de protocoles de traitement néo adjuvant. La stratégie thérapeutique et l'étendue de la résection chirurgicale peuvent, à l'heure actuelle, être adaptée cas par cas, basées sur le type histologique de la tumeur, sa localisation, le stade tumoral et la condition générale du patient. Avec une approche individualisée, la résection chirurgicale pour cancer de l'oesophage peut être curative et peut être considéré comme un pilier principal dans le traitement du cancer de l'oesophage.

Resumen. Por cuanto se percibe un alto riesgo de la esofagectomía y son pobres los resultados a largo término, continúa la discusión sobre el verdadero valor de la resección quirúrgica como fundamento del tratamiento del cáncer esofágico localizado. Los tumores tempranos son crecientemente

tratados por mucosectomía endoscópica o técnicas de ablación mucosal, en tanto que la radioquimioterapia combinada sin cirugía en muchas instituciones ha venido a ser el tratamiento de escogencia para los tumores localmente avanzados. Sin embargo, varios informes recientes y la experiencia de los autores, indican que la resección quirúrgica es hoy segura y que la supervivencia a largo plazo ha mejorado notablemente en las últimas dos décadas. Un número de factores aparecen asociados con la notable reducción en la mortalidad postoperatoria y la mejor supervivencia a largo plazo luego de una resección quirúrgica. Entre ellos están los cambios en la epidemiología, con un incremento en la incidencia del adenocarcinoma, generalmente ubicado en el esófago distal, la debida selección de los pacientes para cirugía, las superiores técnicas quirúrgicas y el mejor manejo perioperatorio y el uso de protocolos de terapia neoadyuvante. La estrategia del tratamiento y la extensión del procedimiento quirúrgico ahora pueden ser amoldados con base en el tipo histológico del tumor, la ubicación del tumor, el estadio del tumor y la condición general del paciente. Mediante un aproche individualizado, la resección quirúrgica del cáncer esofágico puede, predeciblemente, ofrecer curación. Por ello la resección quirúrgica continúa como el pilar principal en el tratamiento exitoso del cáncer esofágico.

References

1. Earlam R, Cunha-Melo JR. Oesophageal squamous cell carcinoma: a critical review of surgery. Br. J. Surg. 1980;67:381–390
2. Muller JM, Erasmi H, Stelzner M, et al. Surgical therapy of oesophageal carcinoma. Br. J. Surg. 1990;77:845–857
3. Wu PC, Posner MC. The role of surgery in the management of oesophageal cancer. Lancet Oncol. 2003;4:481–488
4. Siewert JR, Stein HJ, Sendler A, et al. Esophageal cancer: clinical management. In Kelsen DA, Daly JM, Kern SE, et al., editors, Gastrointestinal Oncology: Principles and Practice, Philadelphia, Lippincott Williams & Wilkins, 2002;261–288
5. Stein HJ, Feith M, Siewert JR. Approach to early Barrett's cancer. World J. Surg. 2003;27:1040–1046
6. Wong RK, Malthaner RA, Zuraw L, et al. Cancer Care Ontario Practice Guidelines Initiative Gastrointestinal Cancer Disease Site Group; combined modality radiotherapy and chemotherapy in nonsurgical management of localized carcinoma of the esophagus: a practice guideline. Int. J. Radiat. Oncol. Biol. Phys. 2003;55:930–942
7. Law S, Kwong DL, Kwok KF, et al. Improvement in treatment results and long-term survival of patients with esophageal cancer: impact of chemoradiation and change in treatment strategy. Ann. Surg. 2003;238: 339–347
8. Hofstetter W, Swisher SG, Correa AM, et al. Treatment outcomes of resected esophageal cancer. Ann. Surg. 2002;236:376–384
9. Ando N, Ozawa S, Kitagawa Y, et al. Improvement in the result of surgical treatment of advanced squamous esophageal carcinoma during 15 consecutive years. Ann. Surg. 2000;232:225–232
10. Ellis FHJ, Heatley GJ, Krasna MJ, et al. Esophagogastrectomy for carcinoma of the esophagus and cardia: a comparison of findings and results after standard resection in three consecutive eight-year intervals with improved staging criteria. J. Thorac. Cardiovasc. Surg. 1997;113: 836–846
11. Siewert JR, Feith M, Werner M, et al. Adenocarcinoma of the esophagogastric junction: results of surgical therapy based on anatomical/ topographic classification in 1,002 consecutive patients. Ann. Surg. 2000;232:353–361
12. Siewert JR, Stein HJ, Feith M, et al. Tumor cell type is an independent prognostic parameter in esophageal cancer: lessons learned from more than 1000 consecutive resections at a single institution in the Western world. Ann. Surg. 2001;234:360–369
13. Orringer MB, Marshall B, Iannettoni MD. Transhiatal esophagectomy: clinical experience and refinements. Ann. Surg. 1999;230:392–403
14. Doty JR, Salazar JD, Forastiere AA, et al. Postesophagectomy morbidity, mortality, and length of hospital stay after preoperative chemoradiation therapy. Ann. Thorac. Surg. 2002;74:227–231
15. Stein HJ, Feith M, Siewert JR. Malignant degeneration of Barrett's esophagus: clinical point of view. Recent Results Cancer Res. 2000;155: 119–122
16. Von Rahden BHA, Stein HJ, Siewert JR. Barrett's esophagus and Barrett's carcinoma. Curr. Oncol. Rep. 2003;5:203–209
17. Stein HJ, Feith M, Mueller J, et al. Limited resection for early Barrett's cancer. Ann. Surg. 2000;232:733–742
18. Stein HJ, Brucher BL, Sendler A, et al. Esophageal cancer: patient evaluation and pre-treatment staging. Surg. Oncol. 2001;10:103–111
19. Bartels H, Stein HJ, Siewert JR. Preoperative risk analysis and postoperative mortality of esophagectomy for resectable esophageal cancer. Br. J. Surg. 1998;85:840–844
20. Stein HJ, Bartels H, Siewert JR. Esophageal carcinoma: 2-stage operation for preventing mediastinitis in high risk patients. Chirurg 2001;72: 881–886
21. Stein HJ, Feith M. Cancer of the esophagus. In Gospodarowicz M, editor, Prognostic Factors in Cancer, Wiley-Liss Inc., New York, 2001; 237–249
22. Birkmeyer JD, Siewers AE, Finlayson EV, et al. Hospital volume and surgical mortality in the United States. N. Engl. J. Med. 2002;346:1128–1137
23. Dimick JB, Cattaneo SM, Lipsett PA, et al. Hospital volume is related to clinical and economic outcomes of esophageal resection in Maryland. Ann. Thorac. Surg. 2001;72:334–339
24. Stein HJ, Theisen J, Siewert JR. Surgical resection for esophageal cancer: role of extended lymphadenectomy. In Fielding JWL, Hallissey MT, editors, Upper Gastrointestinal Surgery, New York, Springer-Verlag, 2004 (in press)
25. Altorki N, Kent M, Ferrara C, et al. Three-field lymph node dissection for squamous cell and adenocarcinoma of the esophagus. Ann. Surg. 2002;236:177–183
26. van de Ven C, De Leyn P, Coosemans W, et al. Three-field lymphadenectomy and pattern of lymph node spread in T3 adenocarcinoma of the distal esophagus and the gastro-esophageal junction. Eur. J. Cardiothorac. Surg. 1999;15:769–773
27. Stein HJ, Sendler A, Fink U, et al. Multidisciplinary approach to esophageal and gastric cancer. Surg. Clin. North Am. 2000;80:659–682
28. Urschel JD, Vasan H. A meta-analysis of randomized controlled trials that compared neoadjuvant chemoradiation and surgery to surgery alone for resectable esophageal cancer. Am. J. Surg. 2003;185:538–543
29. Walsh TN, Noonan N, Hollywood D, et al. A comparison of multimodal therapy and surgery for esophageal adenocarcinoma. N. Engl. J. Med. 1996;335:462–467
30. Medical Research Council Oesophageal Cancer Working Group. Surgical resection with or without preoperative chemotherapy in oesophageal cancer: a randomised controlled trial. Lancet 2002;359:1727–1733
31. Wieder HA, Brücher BLDM, Zimmermann F, et al (2004) Time course of tumor metabolic activity during chemoradiotherapy of esophageal squamous cell carcinoma and response to treatment. J. Clin. Oncol. 22: 900–908
32. Luketich JD, Alvelo-Rivera M, Buenaventura PO, et al. Minimally invasive esophagectomy: outcomes in 222 patients. Ann. Surg. 2003;238: 486–495
33. Law S, Wong J. Use of minimally invasive oesophagectomy for cancer of the oesophagus. Lancet Oncol. 2002;3:215–222
34. Banki F, Mason RJ, DeMeester SR, et al. Vagal-sparing esophagectomy: a more physiologic alternative. Ann. Surg. 2002;236:324–335
35. Kitagawa Y, Fujii H, Mukai M, et al. Intraoperative lymphatic mapping and sentinel lymph node sampling in esophageal and gastric cancer. Surg. Oncol. Clin. N. Am. 2002;11:293–304
36. Kato H, Miyazaki T, Nakajima M, et al. Sentinel lymph nodes with technetium-99m colloidal rhenium sulfide in patients with esophageal carcinoma. Cancer 2003;98:932–939
37. Kitajima M, Kitagawa Y. Surgical treatment of esophageal cancer—the advent of the era of individualization. N. Engl. J. Med. 2002;347:1705–1709