Multimodality Therapy for Esophageal Cancer

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ABSTRACT

Adjuvant and neoadjuvant therapeutic principles have in recent years received increasing attention in the management of patients with esophageal cancer. A series of randomized prospective trials has convincingly demonstrated that adjuvant postoperative radiation or chemotherapy does not result in a survival advantage after a complete tumor resection. The available data on the role of neoadjuvant preoperative therapy in patients with adenocarcinoma or squamous cell carcinoma of the esophagus are not yet conclusive. While neoadjuvant therapy may undoubtedly reduce the tumor mass in a substantial portion of patients, a series of randomized controlled trials has shown that compared with primary resection, a multimodal approach does not result in a survival benefit in patients with locoregional, i.e., potentially resectable, tumors. In contrast, in patients with locally advanced tumors, i.e., tumors in which a complete tumor removal with primary surgery appears unlikely, neoadjuvant therapy allows a marked downstaging of the primary tumor and thus significantly increases the chance for complete tumor removal on subsequent surgery. However, only patients with objective clinical or histopathological response to preoperative therapy appear to benefit from this approach. Compared with preoperative chemotherapy alone, combined radiochemotherapy increases the rate of response but may also increase postoperative morbidity and mortality. Neoadjuvant therapy should therefore currently be performed only in experienced centers within the context of clinical trials. The identification of factors which would facilitate prediction of the response to neoadjuvant therapy is currently the focus of several studies. Furthermore, more effective and less toxic preoperative therapy regimens are required to increase the response rates and combat systemic recurrences.

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INTRODUCTION

In past decades, there have been marked advances in the surgical management of patients with esophageal cancer. Detailed preoperative risk analysis, standardized resection and reconstruction techniques and aggressive perioperative management have reduced postoperative mortality of en bloc esophagectomy with systematic lymph node dissection to below 5% in experienced centers [1-5]. The majority of patients with early esophageal carcinoma limited to the mucosa or submucosa can be cured with this approach. Even in patients with more advanced tumors or early stages of lymphatic spread, the five-year survival rate after surgical resection approaches 40% provided that a complete macroscopic and microscopic tumor resection is performed with sufficient margins in the area of the primary tumor and the lymphatic drainage, i.e., an R0-resection in the International Union Against Cancer (UICC) classification [6], is achieved [1, 2].

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Despite these advances, the overall prognosis of patients with esophageal carcinoma has not improved markedly [7]. This is due to the usually late diagnosis of squamous cell or adenocarcinoma of the esophagus. At the time of presentation, the tumor has usually grown beyond the esophageal wall and extensive lymph node or distant metastases are present. Furthermore, lymph node metastases can already be documented in up to 30% of the patients with early tumors (Fig. 1). Finally, the close anatomic relationship between the proximal esophagus and the tracheobronchial tree frequently prohibits an extensive resection with adequate safety margins in the affected patients [8]. A complete macroscopic and microscopic tumor resection is consequently not possible in the majority of patients presenting with esophageal cancer. Even extended surgical resection usually remains palliative in these patients.

This situation has resulted in an increased interest in neoadjuvant and adjuvant therapeutic modalities, i.e., radiation, chemotherapy or combined radiochemotherapy before or after surgical resection, in the management of patients with esophageal cancer [9-11]. In the following review, the clinical role of these multimodal therapeutic approaches is critically analyzed based on the original published data. Whenever possible, randomized phase III trials were considered. Only where randomized trials were not available were phase II studies also included in the analysis.

Despite the large number of available studies, no firm conclusions can be drawn in most instances. This is because of a series of shortcomings in many studies which have to be taken into account when interpreting the data. In most studies, tumor length is used to stratify the patients, rather than the prognostically more important factor of depth-of-wall penetration. Endoscopic ultrasound, the most accurate tool for assessing wall penetration, is usually not used in the pretherapeutic assessment. Furthermore, adenocarcinoma and squamous cell carcinoma, which biologically represent different tumor entities, are often not separated. In addition, the extent of resection and lymphadenectomy, both of which may influence the prognosis of the patient [1, 2, 4, 5], is usually not standardized, and the postoperative histopathological evaluation of the resected specimen is often not performed according to the criteria of the American Joint Committee on Cancer (AJCC)/UICC [6]. This makes comparison of data between various centers difficult. Despite these shortcomings, a critical evaluation of the available data clearly shows that the tumor type, the pretherapeutic estimation of the resectability of the primary tumor (i.e., locoregional and well-resectable tumors versus locally advanced tumors with doubtful resectability), the clinical response to neoadjuvant therapy and the presence of residual tumor after resection are the major factors that need to be considered when critically evaluating the clinical role of multimodal therapy for esophageal cancer [12, 13].

**ADJUVANT AND ADDITIVE THERAPY**

Postoperative radiation and/or chemotherapy are frequently employed after incomplete tumor resection (R1- or R2-resection [6]) and are also advocated after complete tumor resection (R0-resection). The advantage of postoperative therapy in contrast to preoperative radiation or chemotherapy is that it can be guided by the intraoperative and histopathological findings. Disadvantages of postoperative therapy include the presence of the radiation-sensitive esophageal substitute and the low activity of chemotherapy in postoperative tissue.

The role of postoperative radiation was evaluated in two randomized prospective trials. Both studies failed to show an increase in survival time with postoperative radiation in patients with or without residual tumor after surgical resection [14, 15]. The only benefit from postoperative radiation was improved local tumor control with a 10%-40% reduction in mediastinal recurrences and tracheobronchial fistulae after palliative resections. This was achieved at the expense of significant morbidity and early systemic metastasis in one of these trials. Postoperative radiation should consequently be considered only in patients with residual mediastinal disease after surgical resection in whom the risk of mediastinal recurrence and tracheobronchial fistula is high.

Postoperative chemotherapy is frequently employed to prevent, delay or treat systemic metastases in patients with squamous cell esophageal carcinoma who had a local R0-resection. Controlled trials supporting the use of adjuvant chemotherapy are, however, scarce. In a randomized trial
by the Japanese Oncology Group, postoperative chemotherapy had no beneficial effect compared to postoperative radiation, but was associated with significant side effects and morbidity [16]. This was also confirmed in a recent randomized multicenter study from France. This trial showed no survival difference with or without postoperative chemotherapy in patients who had a curative or palliative resection of squamous cell esophageal carcinoma, while side effects were common and severe in those who received postoperative chemotherapy [17].

Consequently, there is currently no firm scientific basis for adjuvant or additive postoperative radiation or chemotherapy in patients who have undergone resection for esophageal cancer. Palliative postoperative radiation may only be considered in those with macroscopic or microscopic residual tumor (R1- or R2-resection) in whom the risk for a tracheobronchial fistula is high.

**Theoretical and Experimental Basis of Neoadjuvant Therapy**

Due to the lack of effective postoperative protocols, a variety of neoadjuvant preoperative therapeutic modalities has been extensively investigated in recent years in an effort to induce downstaging of the primary tumor, increase the rate of complete tumor resections, eliminate potential systemic micrometastasis and ultimately prolong survival in patients with esophageal carcinoma. There are several theoretical considerations and experimental data that support the use of radiation and/or chemotherapy prior to, rather than after, surgical resection. Experimental studies showed that surgery may induce a growth stimulus for tumor cells left behind after resection [18]. This was manifested by an increased proliferation rate, a marked shortening of tumor doubling time and rapid increase of the size and number of distant metastases [19-21]. The proliferation stimulus may also be associated with an increased rate of spontaneous mutations resulting in clones of chemotherapy-resistant tumor cells [22]. Reduction of the tumor cell mass prior to surgical intervention by chemotherapy or radiation inhibited this proliferation stimulus and markedly prolonged survival in these experimental models [23]. An additional argument supporting the preoperative use of chemotherapy is the altered vascular supply in the surgical field. In contrast to the preoperative situation, postoperative systemic therapy may not reach residual tumor in sufficiently high concentrations.

**Neoadjuvant Therapy for Squamous Cell Esophageal Cancer**

The available data on neoadjuvant treatment in patients with esophageal cancer can be classified into studies assessing preoperative radiation, preoperative chemotherapy or combined preoperative radiochemotherapy, either applied consecutively or simultaneously. Because of the markedly different prognosis and different available therapeutic alternatives, patients with locoregional or potentially resectable tumors must be assessed separately from patients with locally advanced tumors in whom the chance for a complete tumor resection is questionable based on pretherapeutic staging [12, 13]. In patients with potentially resectable tumors, the results of neoadjuvant therapy following by resection have to be compared with the current “gold standard” of primary resection. In contrast, the results of primary surgical resection in patients with locally advanced tumors are dismal. Any therapeutic modality which offers the chance for long-term survival in these patients must be considered a significant benefit.

**Preoperative Radiotherapy**

The use of neoadjuvant radiation is based on the premise of preoperative devitalization, reduction of the tumor bulk and eradication of lymph node metastases. Theoretically, this should increase the resectability, particularly for tumors located in the proximal half of the esophagus, and diminish intraoperative spread of tumor cells. The possible increase of the resection rate and reduction of local recurrences with this approach, however, have to be balanced against a potentially increased perioperative morbidity, and in patients who do not respond to radiation, an unjustifiable delay of potentially curative surgery.

Earlier uncontrolled and retrospective studies suggested a prognostic benefit with preoperative radiation in patients with squamous cell esophageal cancer. Five randomized prospective trials comparing preoperative radiation followed by surgical resection with surgical resection alone have been published (Table 1) [24-28]. Four of these trials could not confirm an increase in the resection rate or effect on survival with preoperative radiation as compared to results for patients who had surgical resection alone [24-27]. The only benefit from preoperative radiation in these studies appeared to be an improvement in local tumor control. Unfortunately, in these studies, patients were not stratified into those with locoregional or locally advanced tumors. In contrast, a Scandinavian randomized multicenter study showed improvement in the prognosis after preoperative radiation as compared to primary resection in patients with locoregional esophageal cancer [28]. The latter study was, however, severely criticized because of low patient numbers in the various treatment arms and grave weaknesses in the study design and data analysis. Consequently, the clinical use of preoperative radiation therapy in patients with esophageal carcinoma cannot currently be justified by randomized trials. Because of recent advances in timing, dosage and delivery of radiation and the supportive effect of radiosensitizing chemotherapeutic agents, additional studies are required to define the role of preoperative radiation in patients with squamous cell esophageal carcinoma.
Preoperative Chemotherapy

At least theoretically, the preoperative use of chemotherapy offers several advantages. In addition to an increase in the resectability by downstaging of the primary tumor, preoperative chemotherapy allows early systemic treatment of distant micrometastases which may be present even in patients with less-advanced disease. Furthermore, the efficacy of various cytotoxic agents can be tested in the individual patient. The results of these tests can be used as a guide for the selection of postoperative additive or adjuvant therapy.

The vast majority of studies on preoperative chemotherapy in patients with potentially resectable tumors have been single-arm uncontrolled phase II trials. Taken together, these studies indicate that preoperative chemotherapy in patients with potentially resectable esophageal carcinoma is feasible and does not appear to increase postoperative morbidity and mortality. Depending on the preoperative chemotherapy protocol employed, a complete or partial clinical response was observed in 14%-71% of the patients, with subsequent R0-resection in 36%-83%. A complete histopathological response after preoperative chemotherapy was rare. When compared to results on a series of patients with equally advanced esophageal carcinoma who had primary resection at our institution, preoperative chemotherapy does not appear to improve overall survival [9, 12]. This was confirmed in six prospective randomized trials (Table 2) [29-33]. Compared to primary surgical resection, preoperative chemotherapy did not increase the resection rate, rate of R0-resections or survival time in these studies. In none of the phase III trials did the rate of complete pathological responses to preoperative chemotherapy exceed 10%. A survival advantage with preoperative chemotherapy could only be demonstrated in the subgroup of patients who responded to preoperative chemotherapy. Preoperative chemotherapy in patients with potentially resectable tumors must therefore be considered investigational.

### Table 2. Randomized prospective studies comparing preoperative chemotherapy followed by surgical resection with primary resection in patients with potentially resectable esophageal carcinoma

<table>
<thead>
<tr>
<th>Author</th>
<th>Treatment modality</th>
<th>Number of patients</th>
<th>Clinical response</th>
<th>Complete histopathological response</th>
<th>Postop mortality</th>
<th>Median survival</th>
<th>2-year survival</th>
<th>5-year survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Roth et al. [29]</td>
<td>Surgery alone</td>
<td>19</td>
<td>–</td>
<td>–</td>
<td>0%</td>
<td>9 months</td>
<td>5% (3-year)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDDP-BL-VDS + Surgery</td>
<td>17</td>
<td>47%</td>
<td>6%</td>
<td>12%</td>
<td>9 months</td>
<td>25% (3-year)</td>
<td></td>
</tr>
<tr>
<td>Schlag et al. [30]</td>
<td>Surgery alone</td>
<td>41</td>
<td>–</td>
<td>–</td>
<td>10%</td>
<td>9 months</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDDP-5-FU + Surgery</td>
<td>34</td>
<td>41%</td>
<td>6%</td>
<td>19%</td>
<td>8 months</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Nygaard et al. [28]</td>
<td>Surgery alone</td>
<td>41</td>
<td>–</td>
<td>–</td>
<td>13%</td>
<td>–</td>
<td>3% (5-year)</td>
<td>9% (5-year)</td>
</tr>
<tr>
<td></td>
<td>CDDP-BL + Surgery</td>
<td>50</td>
<td>–</td>
<td>–</td>
<td>15%</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Kok et al. [31]</td>
<td>Surgery alone</td>
<td>80</td>
<td>–</td>
<td>–</td>
<td>4%</td>
<td>12 months</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDDP-5-FU + Surgery</td>
<td>80</td>
<td>51%</td>
<td>7%</td>
<td>2%</td>
<td>12 months</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Fok et al. [32]</td>
<td>Surgery alone</td>
<td>26</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>10 months</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDDP-Etop + Surgery</td>
<td>48</td>
<td>42%</td>
<td>–</td>
<td>–</td>
<td>14 months</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td>Ancona et al. [33]</td>
<td>Surgery alone</td>
<td>38</td>
<td>–</td>
<td>3%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CDDP-5-FU + Surgery</td>
<td>36</td>
<td>8%</td>
<td>9%</td>
<td>–</td>
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</table>
Despite the usually late presentation of patients with squamous cell carcinoma, randomized trials comparing preoperative chemotherapy to primary resection in patients with locally advanced squamous cell esophageal cancer are still lacking. Taken together, the data from the available phase II studies show that as in patients with potentially resectable tumors, preoperative chemotherapy is also feasible in patients with locally advanced esophageal carcinoma, but appears to improve the prognosis only in those patients who respond to preoperative treatment.

**Preoperative Combined Radiochemotherapy**

The low rate of complete pathological responses with preoperative chemotherapy alone prompted several groups to assess a combination of preoperative chemotherapy with radiation. A review of the literature shows several initial studies using a variety of chemotherapeutic agents in combination with a wide range of radiation doses, while most of the recent studies are based on a combination of cisplatinum with 5-fluorouracil (5-FU) and 30-40 Gy of radiation [9, 12]. In these studies, the concurrent use of preoperative radiation and chemotherapy resulted in complete pathological response rates ranging between 20% and 42%. These were, however, achieved at the expense of an increase in morbidity and postoperative mortality which exceeded 20% in some of the studies.

Despite the impressive response with combined radiochemotherapy, the results of the available randomized phase III studies comparing preoperative combined radiochemotherapy with primary surgical resection in patients with potentially resectable tumors do not show an increase in the R0-resection rate or a clear overall survival benefit with preoperative therapy [34-36]. Any beneficial effect of neoadjuvant radiochemotherapy in patients with potentially resectable tumors appears to exist only in the subgroup of patients with clinical or complete histopathological response to preoperative therapy. Since clinical and histopathological responses cannot currently be reliably predicted based on pretherapeutic parameters, preoperative radiochemotherapy in patients with potentially resectable tumors should not be performed outside the context of clinical studies.

The experience with studies assessing preoperative radiochemotherapy in patients with locally advanced squamous cell esophageal carcinoma is limited. The few available phase II studies indicate that preoperative combined radiochemotherapy may lead to a marked downstaging of the tumor in a significant number of patients and thus allow subsequent complete tumor resection [9]. In our experience, a three-week course with 5-FU chemotherapy given as continuous infusion simultaneously with 30 Gy radiation allowed subsequent complete resection in over 80% of 55 patients who had a locally advanced squamous cell esophageal carcinoma located at or above the level of the tracheal bifurcation [37]. Compared to primary resection for similarly advanced tumors, neoadjuvant radiochemotherapy significantly improved the prognosis in this study (Fig. 2). Detailed analysis, however, showed that the prognostic gain was limited to those who had an objective tumor remission and subsequent complete resection. In all other patients, this neoadjuvant approach was associated with significant morbidity and mortality but no prognostic benefit.

**Neoadjuvant Therapy for Adenocarcinoma of the Esophagus**

The prevalence and incidence of adenocarcinoma of the distal esophagus has shown a marked rise in past decades; in some centers of the Western world, this adenocarcinoma now equals or outnumbers squamous cell esophageal carcinoma. Although esophageal adenocarcinoma and squamous cell carcinoma are different tumor entities epidemiologically and biologically, they are not separated in most neoadjuvant treatment trials. Studies solely investigating neoadjuvant therapy in patients with adenocarcinoma of the esophagus are scarce and their results contradictory [38-41]. The single available randomized phase III study in patients with adenocarcinoma of the esophagus compares preoperative combined radiochemotherapy with primary resection in patients having potentially resectable tumors [42]. The results of this

**Figure 2. Cumulative survival rate with primary resection versus neoadjuvant radio-chemotherapy (RCTx) with subsequent resection in patients with locally advanced squamous cell carcinoma of the esophagus located at or above the level of the tracheal bifurcation (data from ongoing study at TU München) [37].**
study are available as interim analysis in abstract form only. This analysis demonstrates a marked downstaging and a significant survival benefit with combined neoadjuvant radiochemotherapy as compared to primary resection. However, until the final results of this study are available and confirmed by other investigators, primary resection remains the treatment of choice for patients with potentially resectable adenocarcinoma of the distal esophagus.

In our practice, neoadjuvant therapy in patients with adenocarcinoma of the esophagus is restricted to those with locally advanced tumors in whom, based on preoperative staging, an R0-resection appears questionable. The neoadjuvant therapy regimen used is derived from studies assessing combined modality treatment of gastric cancers rather than squamous cell esophageal carcinoma [43]. Our experience with this approach shows that neoadjuvant therapy with a cisplatin-based polychemotherapy regimen followed by surgical resection markedly improves survival in patients with locally advanced adenocarcinoma of the esophagus as compared to patients in similarly advanced tumor stages who had a primary resection (Figure 3) [44]. Follow-up of these patients, however, showed a rather high rate of locoregional tumor recurrences, suggesting that a combination of preoperative chemotherapy with radiation must be considered in future studies.

**Patient Selection for Neoadjuvant Therapy**

Based on this analysis, the choice of therapy for esophageal cancer should be guided by the resectability of the tumor and the physiological status of the patient [13, 45]. Resectability can best be assessed by endoscopic ultrasonography. Estimation of the risk requires a detailed analysis of cardiac, pulmonary, hepatic and renal functions and an assessment of the cooperation of the patient. In patients with tumors confined to the esophageal wall on endoscopic ultrasonography, i.e., patients in whom an R0-resection can be anticipated with a high degree of certainty, primary resection is the treatment of choice, provided that their physiological status permits an extensive surgical procedure. In patients with locally advanced tumors, i.e., patients in whom an R0-resection is questionable, neoadjuvant therapy should be initiated with the aim of downstaging the primary tumor and increasing the chance for a complete tumor resection on subsequent surgery. Due to the potential for increased mortality and morbidity with this approach, however, surgical resection after preoperative neoadjuvant therapy should be restricted to those who respond to preoperative therapy and who have sufficient physiological reserve to withstand a potentially prolonged and complicated postoperative course. In patients with a locoregional or locally advanced esophageal carcinoma and poor physiological status, the expected high perioperative mortality does not justify combined modality therapy or primary resection. Conservative measures, e.g., combined definitive radiochemotherapy, should therefore be initiated in these patients.

**Open Questions in Neoadjuvant Therapy**

**Selection of the Neoadjuvant Therapeutic Modality**

Careful long-term follow-up of patients who had neoadjuvant therapy followed by surgical resection shows that control of distant disease remains a major problem. Even patients with no viable tumor in the resected specimen may die from systemic disease three years or longer after surgical resection. Current neoadjuvant modalities, therefore, appear to delay the occurrence of distant metastasis rather than cure systemic disease. Consequently, more effective and less toxic preoperative chemotherapy regimens are needed to combat systemic sites of esophageal cancer. Improvement in the control of distant tumor growth may in the future be achieved by intensifying the chemotherapy component in the combined modality approach. Supportive use of G-CSF or GM-CSF to increase the dose intensity per treatment time and an alteration in the sequence of radiation and chemotherapy with the aim of delivering more systemic chemotherapy prior to combined radiochemotherapy are the most promising approaches for achieving this goal. One such study assessed whether the development of systemic metastases can be prevented or delayed without a loss in local tumor control by the use of...
intensive primary chemotherapy followed by radiochemotherapy and subsequent resection. Initial results with this sequential approach are promising [46]. Because of the excessively long preoperative treatment phase and the associated burden for the patient, the long-term results of this study must be awaited before this approach can be recommended.

**Assessment of Response to Neoadjuvant Therapy**

Most available studies show that a prognostic benefit from multimodal therapy can be expected only in patients who respond to preoperative therapy and who have a subsequent complete tumor resection. Treatment-related morbidity and mortality are excessive, and the prognosis is dismal in those who do not respond to neoadjuvant therapy. Consequently, a surgical resection after neoadjuvant therapy should only be performed if a complete tumor resection can be anticipated. Parameters that would facilitate prediction of the response to neoadjuvant therapy and subsequent R0-resection are, therefore, clearly needed to avoid the morbidity and mortality associated with combined modality treatment in patients who may not receive any benefit from this approach.

The matter is complicated, however, by the observation that none of the commonly available pretherapeutic data allow prediction of clinical or histopathological response to neoadjuvant therapy. In addition, clinical response frequently does not relate to histopathological response. Residual tumor is often found in the resected specimen in patients who had a complete clinical response, while up to 20% of patients with only partial or no clinical remission may have a sterilized specimen. Endoscopic ultrasonography does not aid in the assessment of response to neoadjuvant therapy either because the echo pattern of residual tumor cannot be differentiated from the sequelae of radiation and chemotherapy [47]. Consequently, additional research must focus on parameters that facilitate the identification of patients who might benefit from neoadjuvant therapy and that improve the assessment of response prior to resection. Potential markers that are currently under investigation include the endoscopic growth pattern of the tumor and several subcellular and molecular markers of the tumor cells. Positron emission tomography is currently also under investigation as a tool for assessing response to neoadjuvant therapy.

**Role and Extent of Surgical Resection after Neoadjuvant Therapy**

The potentially increased risk of esophageal resection after neoadjuvant therapy has prompted several investigators to question the role of surgical resection after chemotherapy or radiochemotherapy. Several recent studies show that in contrast to patients who had neoadjuvant therapy followed by resection, patients who have radiochemotherapy alone commonly exhibit local tumor recurrences [48, 49]. Surgical resection therefore remains an essential component of the combined-modality approach to treating esophageal cancer. However, at the present time it is unclear whether a surgical resection should be performed on all patients receiving neoadjuvant therapy or only on those who respond to neoadjuvant therapy. The optimal timing of surgical resection, i.e., immediate surgery after recovery of neoadjuvant therapy or surgery as salvage therapy, has not been properly assessed. Furthermore, the extent of resection and lymphadenectomy after neoadjuvant therapy remains controversial. In order to definitely answer these questions, carefully designed further-randomized prospective trials are essential.

**REFERENCES**


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