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Tumour control and dysphagia improvement in patients with locally advanced T3/ T4 oesophageal squamous cell cancer after definitive radio-chemotherapy

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Introduction. Squamous cell carcinoma of the esophagus (scc) is usually diagnosed in an advanced stage resulting in limited curative options. The aim was to evaluate immediate and long-term effects of combined chemo-radiotherapy of loco-regionally advanced scc in terms of dysphagia relief and tumour response.
Material and methods. Between 1997 and 2000, 35 pts with scc completed full definitive non-surgical treatment. Men – 31, women – 4; mean age: 51. Tumour stage: T4 – 5, T3 – 30, node stage: N0 – 8, N1 – 27; dysphagia at presentation: WHO III° – 17%, II° – 46%, I° – 37%. Irradiation: conventional fractionation to a dose of 56-60 Gy to tumour, 54-60 Gy to enlarged lymph nodes, 40-44 Gy electively to regional lymph nodes in combination with 2 courses of i.v. chemotherapy: 5-fluorouracil: 800 mg/m^2/24h (day: 1-4, 22-25), cisplatin: 80 mg/m^2 (day: 1, 22) followed by HDR brachytherapy boost using ^{192}Ir – 6 Gy after a one week interval. During follow-up the patients were scored according to the swallowing function, weight change and pain control. Tumour regression and late radiotherapy side effects were observed.
Results. Initial improvement in dysphagia occurred in 20/35 patients (57%) during treatment. Durable improvement at 1-year was evidenced in 19/35 (54%) pts. 31% were dysphagia-free at 1 year. Average duration of dysphagia improvement was 11 months. Only patients with marked improvement in the swallowing function documented during treatment were able to maintain this function for a longer time. We achieved an overall response rate to treatment of 52%. CR (local control) was noted in 26% of pts and local progression (PD) in 34% at 12 months. The median time to tumour progression was 5.4 months. Systemic failure was noted in 20% of patients. The median time to metastases was 8 months and median survival – 12.5 months with a 1-year observed survival of 54%, 2-year– 31% and 3-year – 23%.
Conclusions. 1. Primary concurrent chemo-radiotherapy for advanced T3/T4 N0-1 scc of the oesophagus seems to be a reasonable modality to control short- and long-term dysphagia and pain. 2. The rate and degree of the initial improvement of the swallowing function is a good prognostic tool for assessing the long-term swallowing status. 3. Relatively low local control rate of 26%, due to advanced stage of the disease in our patients, indicates the need for further evaluation of a more efficient treatment modality in this tumour with poor prognostis.

Key words: esophageal cancer, radiotherapy, combined treatment

Introduction

In most countries world-wide, except for Japan, squamous cell carcinoma of the esophagus (scc) is usually diagnosed in advanced stage (III°, IV°) of the disease. This results in limited curative options due to low resectability/operability rates and poor prognosis for patients (pts) with T3/T4 N0-1 scc and usually directs treatment intention to a palliative setting. The main objectives of treatment are, therefore, local control and palliation of dysphagia.

Based on the positive results from the Herskovic trial [1], as well as on other randomised studies [2-4] concurrent chemotherapy and radiotherapy became recognised as effective treatment modalities for loco-regionally advanced scc. However, despite multiple efforts for improving results of conservative treatment, definitive chemo-radiotherapy is still associated with a high rate (about 50%) of locally persistent or recurrent disease [5-8].

We have undertaken this study with the aim of evaluating immediate and long-term effects of combined chemo-radiotherapy in loco-regionally advanced scc in terms of dysphagia relief, tumour response, pain control and weight gain.

Material

From June 1997 to October 2000, 57 pts with histologically proven T3/T4, N0-1 scc underwent conservative treatment with radiotherapy or radio-chemotherapy at The Madame Sklodowska-Curie Memorial Cancer Centre and Institute of Oncology in Warsaw.

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These patients were not candidates for primary surgery due to either the localisation of the tumour in the cervical oesophagus or advanced local disease or potential high morbidity due to pre-existing general health conditions. A few patients also refused offered surgery. 35 patients were treated with a phase II study protocol of combined radio and chemotherapy and managed to complete the full treatment course. The remaining 22 patients were ultimately treated palliativly due to intercurrent diseases or deterioration of the performance status during treatment.

The primary and secondary aims of the study were: feasibility of the proposed combined treatment, local control, overall survival, disease free survival, patterns of failure as well as improvement in swallowing function and it's durability. We finally evaluated 35 patients treated according to the protocol. Mean age was 51 years, range: 21 – 73 years. Median weight loss before treatment was 6.1 kg (range: 0-17 kg).

Patient characteristics are presented in Table I.

Table I. Patient characteristics

	Number	%
Men	31/35	88.5%
Women	4/35	11.5%
Tumour stage:		
T3	30/35	86%
T4	5/ 35	14%
Node stage:		
N0	8/35	23%
N1	27/35	77%
M1LYM	7/35	20%
Tumour site:		
upper	7/35	20%
middle	13/35	37%
lower	15/35	43%
Performance status WHO:		
1°	31/35	89%
2°	4/35	11%
Dysphagia at presentation (WHO):		
1°	13/35	37%
2°	16/35	46%
3°	6/35	17%

Methods

The patients were irradiated using conventional fractionation to a dose of 56-60 Gy delivered to the tumour, 54-60 Gy selectively delivered to enlarged lymph nodes and 40-44 Gy electively delivered to regional lymph nodes. Radiotherapy was combined with 2 courses of iv. infusion chemotherapy consisting of: 5-fluorouracil 800 mg/m^2/24h (day: 1-4, 22-25), cisplatin 80 mg/m^2 (day: 1 and 22) and followed by a high dose rate brachytherapy boost using ^{192}Ir – single application of 6 Gy after one week interval.

During follow-up patients were scored according to the swallowing function. Weight change and pain control were noted. Esophagogram, gastroscopy and CT scan were performed to estimate tumour regression as well as late radiotherapy effects.

Results

Swallowing status

Pre-treatment swallowing function of the patients is shown in Table II. Dysphagia to solids is scored as mild degree – 1°, difficulties in swallowing semisolids means moderate dysphagia – 2°, dysphagia to liquids is of severe degree – 3°. All analysed patients presented with dysphagia and in 17% of cases it was of severe degree. The pre-treatment and the post-treatment swallowing function was determined using this scoring system and is shown in Table II.

Table II. Dysphagia scale used in assessing swallowing ability in treated patients. Status before and after treatment

Swallowing scale	Pre-treatment status No./(%)	Maximal improvement status No./(%)
No dysphagia – 0°	0	11 (31%)
Mild dysphagia – 1°	13 (37%)	8 (23%)
Moderate dysphagia – 2°	16 (46%)	9 (26%)
Severe dysphagia – 3°	6 (17%)	7 (20%)

A change in swallowing status was defined as increase or decrease in the swallowing score by one or more grades from the initial status. Initial improvement in dysphagia occurred in 20/35 patients (57%) during the 6 weeks of combined treatment. No change was noted in 8 patients, deterioration in swallowing function in 7 patients (Figure 1.). Further downstaging of dysphagia within 1-7 months after radiotherapy was observed in 14/35 patients (40%). Durable improvement at 1-year follow up was evidenced in 19/35 – 54% of patients. 31% of all the patients treated were dysphagia-free at 1 year (65% of the 1-year survivors). Minimal duration of dysphagia improvement was 23 days, maximal – 44.7 months; average – 11 months.

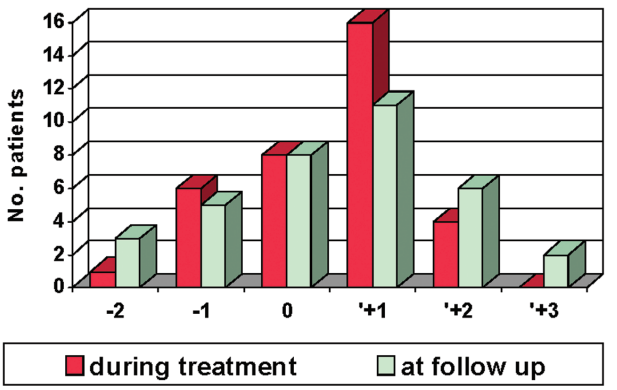

Figure 1. Change in the swallowing status defined as an increase or decrease in the swallowing score by one or more grade from the pre-treatment swallowing score. Overall improvement of the swallowing status was observed in 20/35 (57%) of patients during treatment. 19/35 (54%) of patients maintained improved swallowing status at one year

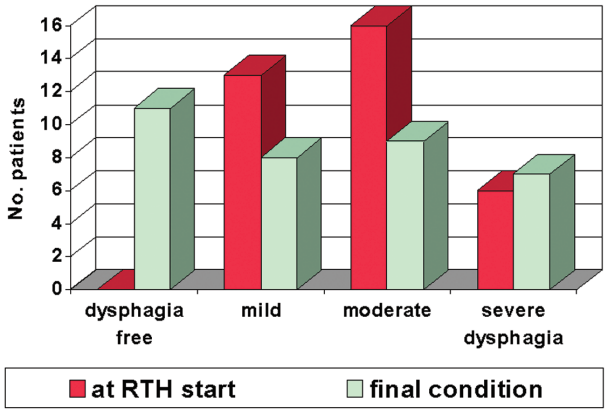

Figure 2. The distribution of patients by dysphagia score. 31% of patients (all after immediate marked improvement) had complete restoration of their ability to swallow solids after therapy

Only patients with initial marked improvement in the swallowing function during treatment were able to maintain this function for a longer period of time. In a retrospective analysis the overall number of patients with changes in the swallowing score by one or more units was determined and it is shown on Figure 2. Further change in the swallowing function was evaluated during follow-up at monthly intervals.

Assessment of long-term swallowing function in patients with advanced disease is limited by their relatively short survival. That is why the observation period in patients with progression after treatment was limited to one year. Figure 3 shows the results of a one-year follow-up of thr dysphagia stage in 12 patients out of 35 (34%) who presented with deterioration in the swallowing status.

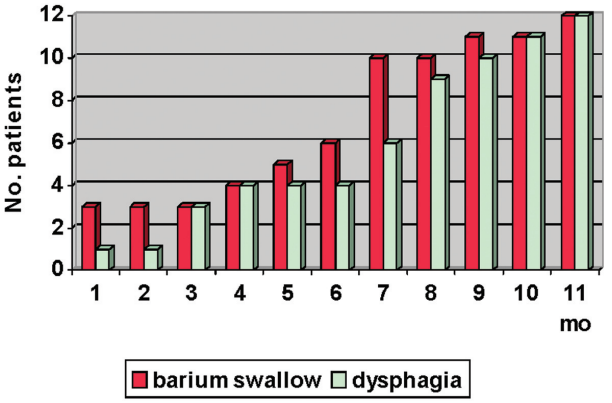

Figure 3. Subjective and objective deterioration of swallowing as a function of time. Estimated each month following completion of treatment. 12/35 of patients (34%) presented growing difficulties in swallowing associated with tumour progression

Tumour control

All follow-up assessments were performed regularly every 1 month for a year then at 3-month intervals.

The tumour response was assessed by radiographic criteria (barium contrast, CT) and endoscopy, with biopsy if possible. Complete regression (CR) was recognised if no evidence of tumour presence could be seen during barium contrast examination and endoscopy. Partial regression (PR) was defined as a decrease by more than 50% of maximum tumour size. Stable disease (SD) was regarded if there was a decrease in the tumour mass by less than 50% or an increase of not more than 25%. Local progression (progression disease PD) was recognised if progression by more than 25% of the tumour size was documented either within the primary tumour or local/regional nodes. Systemic relapse (PD) was defined as any evidence of distant metastases.

Overall response rate to treatment was 52%, CR (local control) was seen in 26% of patients at one year (Table III). Local progression (PD) after treatment was observed in 17% of patients at 6 months, and in 34% at 12 months. Median time to tumour progression was 5.4 months. Systemic failure was noted in 20% of patients. Median time to metastases was 8 months.

Table III. Treatment result at one year assessed by endoscopic and radiographic criteria

Outcome	Number of patients	Percent
complete regression (CR)	9/35	26%
partial regression (PR)	9/35	26%
no change (SD)	5/35	14%
local progression (PD)	12/35	34%
systemic relapse (PD)	7/35	20%

Toxicity

Acute complications

The 35 patients of the analysed group were able to tolerate full doses of radiation and chemotherapy according to the protocol. The tolerance of the combined modality therapy was good. There were no toxic deaths. Severe oesophagitis (Grade 3 according to CTC criteria) occurred in 3% of patients, moderate (Grade 2) in 31%. They did not require interruption or delay in treatment and the observed complications responded well to medical treatment. Severe haematological toxicity was noted in 17% of patients and in this group treatment had to be temporarily withheld.

Average weight loss recorded during treatment was 1.5 kg.

Late complications were of paramount importance in these patients since they influenced their ability to swallow. The total complication rate at one year was 25%. 4/35 (11%) patients developed moderate or severe strictures requiring dilatation, 5/35 (14%) patients developed a tracheo-esophageal fistula requiring endo_ prosthesis placement. All but one case of fistula were treatment-related (in tumours initially staged as T3).

The weight change correlated with the swallowing function and tumour progression. Average weight gain at follow-up was 2.8 kg (range: -4 – +10 kg).

Treatment resulted in good pain control. Only 5 out of 35 patients (14%) required opioid analgesics during follow-up after treatment.

Survival

For the total group of 35 patients median survival was 12.5 months, 1-year observed survival was 54%, 2-year – 31%, 3-year observed survival achieved 23%.

Discussion

Advanced T3/T4, N0-1 oesophageal scc is inevitably associated with poor prognosis and still constitutes a challenge for both surgeons and oncologists. Patients presenting with this disease, who are unfit for primary surgery, are referred for conservative multimodality treatment schedules. This is common clinical practice supported by the results of several clinical trials [1, 6, 7, 9, 10]. In fact, as far as surgery is concerned, only few patients are good candidates for such anapproach. Therefore, in most cases definitive conservative treatment ends up with a generally palliative effect due to loco-regional treatment failure. Even in randomised trials of concurrent chemo-radiotherapy [3, 5, 8] the rate of local failure reached 50%. Effective delivery of an adequately high total dose of irradiation is complicated by anatomic constrains, as well as by the co-morbidity of patients with this disease. Attempts to achieve effective local control and long-term survival with combined treatment (eg. surgery plus chemo-radiotherapy) are limited to stage I and II of the disease.

The goals of conservative management in palliative setting are: relief of pain, maintenance of oral food intake, elimination of reflux and regurgitation, prevention of aspiration. The main goals of definitive treatment with combined radiotherapy and chemotherapy are: long term local control and improved overall and disease-free survival.

In our study patients were irradiated to a 60 Gy total dose by external beam radiotherapy with concurrent chemotherapy and a 6 Gy intraluminal brachytherapy boost. The presented combined regime was feasible and in patients who had completed the full treatment course provided improvement of dysphagia in 54%, with long term local control of cancer in 26%.

In order to enhance the local control rate for advanced cancer a combination of radiotherapy and chemotherapy with an HDR brachytherapy boost was applied. This treatment strategy seemed promising with manageable toxicity and a treatment-related acute complication rate of 4-8% [11-13]. However, in our study the contribution of the brachytherapy boost to the long-term tumour regression is ambiguous. Also the rate of late complications is relatively high – 12% of treatment related fistulae discourages the further use of the radiotherapy boost. Other studies [10, 14, 15] have reported a similar fistula rate after combined treatment, suggesting a cautious approach to the brachytherapy boost after high dose external irradiation.

The presented treatment schedule provides prompt and substantial improvement in swallowing in most patients treated for oesophageal cancer. However, tumour regression during and after treatment, manifested subjectively as marked improvement in the swallowing function was, in most cases, not enough to provide long-term local control of tumour growth. Clinical predictors of good response to chemo-radiotherapy were immediate dysphagia improvement together with objective improvement barium contrast radiological results obtained at the end of the radiotherapy course.

The local recurrence rate after non-surgical treatment of oesophageal cancer has been reported to be between 40%-60% [1, 7]. The local failure rate in our study was 48% at one year. Since most of the failures occur during the first year [5, 14, 16] this seems to be a reasonably good result.

Complete responders after conservative treatment can't be accurately identified by clinical methods. That is why only long-term survivors could be regarded as cured from cancer. Only in their case the maintenance of good swallowing function could become a simplified indicator of local control. As it has already been stated by other authors [17] the rapid restoration of the swallowing status (during treatment) is of important prognostic value for durable tumour control in these patients.

We have performed a retrospective survival analysis of the treated patients. Median survival for the entire group was 12.5 months with a 12-, 24- and 36-month survival rate of 54%, 31% and 23% respectively.

Literature data show similar results. 20% of patients who had received combined modality therapy in the Herscovic trial were alive at 3 years [5].

Minsky [7] has reported a 3-year actuarial survival of 30% and median survival of 20 months. He treated 38 patients with neoadjuvant chemotherapy followed by concurrent chemo-radioterapy and reached the rate of 47% of complete remission after therapy. It is worth stressing that only 34% of patients in his group were diagnosed with T3 tumours. The local/regional failure rate in that trial amounted to 39%.

In another RTOG trial [10] median survival was 11 months with a 2-year survival of 31%.

3-year actuarial survival as reported by Calais [14] equalled 27%, with a local control rate of 57%. Local or regional failure was noted in 43% of patients, with median time to local failure of 8 months and median time to distant metastases of 11 months. A closer look at the stratification of patient data reveals that among the 53 patients treated only 55% presented with a T3/T4 tumour.

In a prospective phase III radiotherapy dose-escalation study by Minsky [8] local failure and persistence of disease exceeded 50%, with 2-year survival of 31% and 40%, respectively, in the two treatment arms (total dose of 50.4 Gy vs 64.8 Gy in 1.8 Gy per fraction). In this randomised trial 44% and 49% of patients,

respectively, out of the 109 treated in each arm presented with T3/T4 tumours.

Gill [18] has observed complete remission in 50% of patients after treatment. Similarly, Chan [16] achieved local control in 68%. In his material stage III disease was diagnosed in only 30% of patients and there were no T4 tumours. The 2-year survival for this subgroup was 25%.

In a study performed by Coia [17] 25/102 (25%) patients presented with local control over 1 year. This result is similar to ours. Coia reported comparable improvement in the swallowing function for palliative as for curative cases in his study, with a median survival time of 8 months.

In an RTOG trial [10], where BRT treatment was applied after external beam irradiation, a local/regional failure rate of 63% was observed; oesophageal stricture was found in 10% of cases with the crude fistula rate of 12%, and the cumulative fistula incidence by the end of the first year of 17.5%. These results are also similar to those observed in our study group.

Patients with advanced T3/T4 tumours are generally referred for palliative treatment. Those in better general condition are included in trials and pooled with less advanced cases. The results of our study, performed on a patient group with T3/T4 tumours, indicate that in case of patients not eligible for surgery, combined non-surgical treatment with radical intent can provide substantial improvement in dysphagia in over half of advanced oesophageal cancer patients and in 26% of them it results in complete tumour regression and normal long-term swallowing function. In case of patients with a good performance status, in whom local disease is too advanced to be referred for surgery, an attempt to administer a prolonged course of combined concurrent primary chemo-radiotherapy seems justifiable.

Conclusions

1. Primary concurrent chemo-radiotherapy for advanced T3/T4 N0-1 scc of the oesophagus seems to be a reasonable modality to control short- and long-term dysphagia and pain.
2. The rate and degree of initial improvement in swallowing function is a good prognostic tool for the assessment of long-term swallowing status.
3. Relatively low local control rate of 26%, due to advanced stage of the disease in our patients, indicates the need for further evaluation of more efficient treatment modality in this poor prognostic cancer.

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