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FROM THE DEPARTMENTS OF RADIATION THERAPY, SURGERY, GASTRO-ENTEROLOGY, ENT AND MEDICAL ONCOLOGY, ROTTERDAM RADIO-THERAPEUTIC INSTITUTE/DAN. DEN HOED CLINIC, ROTTERDAM, AND THE ACADEMIC HOSPITAL, ROTTERDAM-DIJKZIGT, THE NETHERLANDS.

THERAPY OF ESOPHAGEAL CARCINOMA

Results from the Joint Group on Esophageal Carcinoma in Rotterdam

J. G. VAN ANDEL, J. DEES, W. M. H. EIJKENBOOM, H. VAN HOUTEN, J. J. JOBSEN, H. J. MUD, H. OBERTOP and W. L. J. VAN PUTTEN

M. van Blankenstein, M. Eeftinck Schattenkerk, P. C. de Jong, P. Knegt, T. A. W. Splinter and J. Verweij

Abstract

During the period 1978–1981 172 patients were referred to the Rotterdam Joint Group on Esophageal Carcinoma. Ninety-one patients were considered for combined therapy, comprising radiation therapy and surgery, and 10 patients refused surgery. The figures given in this material are actuarial survival values corrected for intercurrent death (the actuarial overall survival in parentheses). The 4-year survival in 69 patients who completed this treatment was 39 per cent (26%) (significantly better for women compared with men; significantly better for tumors <2 vertebrae compared with tumors ≥2 vertebrae). The resectability rate was 85 per cent and the operation mortality rate 20 per cent. Thirty-eight patients had curative radiation therapy with a 4-year corrected survival of 5 per cent (3%). For palliative treatment, radiation therapy and endoscopic introduction of a Celestin tube were mostly used. The results of curative as well as of palliative treatment of esophageal carcinoma have shown improvement during the past decade compared with an earlier period.

Key words: Esophagus, carcinoma, radiation therapy, surgery.

Treatment of carcinoma of the esophagus aims at preserving or ameliorating food passage and if possible curing the patient.

The curative results of radiation therapy are not satisfactory. CUCINGNAN & CAREY (4) reported a 5-year survival of 4 to 7 per cent in a collective review. In materials of cervical esophageal carcinoma (which often include postcricoid hypopharyngeal cancer) the results are better than in the other locations, and a 5-year survival of 15 to 30 per cent has been reported (23, 24, 26). The results of surgical management seem to be somewhat better than those of radiation therapy alone, but there is a high operative mortality. CUCINGNAN & CAREY (4) reported a 5-year survival of 2 to 21 per cent in their review. Because of these disappointing results combined radiation therapy and surgery has been applied in several centres (1, 2, 7, 13, 21, 22, 25, 27, 30).

In the past few years, chemotherapy has also been included in different combinations with radiation therapy and surgery (12, 15, 16, 17, 28). Preoperative irradiation aims at decreasing the bulk of the tumor and reducing or irradicating the cancerous infiltration of the surrounding tissues or organs, thereby increasing the resectability. Moreover, after preoperative radiation therapy the possibility of local seeding and distant dissemination caused by the operative manoeuvres may be reduced (5, 10, 11, 29, 31).

The Joint Group on Esophageal Carcinoma of the Rotterdam Radio-Therapeutic Institute and the Academic Hospital Rotterdam-Dijkzigt (RRTI/AZR-D) has chosen a schedule of combined radiation therapy and surgery in the treatment of esophageal cancers with a curative intention. The results from 172 patients treated in the period 1978–1981 are discussed.

Material and Methods

The following principles were applied by the Group. If curative treatment was to receive consideration, the tumor had to be theoretically curable, i.e. thorough exami-

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nation should not reveal fixation to neighboring structures, growth through the wall or into surrounding tissues, or distant metastases. Moreover, the patient had to be operable, which meant that his condition should permit preoperative irradiation and a combined thoraco-laparotomy. The biologic age and the cardio-pulmonal situations were therefore very important. The extensive pretreatment analysis could be performed within one week.

In order to obtain information regarding the local tumor the examination schedule included radiography of the esophagus and stomach, esophagoscopy with biopsy, and histologic examination. For information on infiltration or metastases the following measures were applied: Clinical examination with special attention to detection of metastatic cancer and to cardiovascular and pulmonary status; ECG and routine laboratory tests; pulmonary function tests; radiography of the thorax; ultrasonography of the upper abdomen; CT of thorax and upper abdomen; laryngoscopy (function of vocal cords); bronchoscopy with puncture of subcarinal nodes for cytology; and laparoscopy when the tumor was located in the distal esophagus.

In the period 1978–1981, 172 patients (122 males and 50 females) were examined in this way. The histology was squamous cell carcinoma in 64 per cent, adenocarcinoma in 30 per cent and other forms were present in 6 per cent. In one patient, the tumor was not histologically classified (Table 1). At the end of this analysis 91 patients were thought to be theoretically curable and operable, and could be considered for combined treatment with curative intention.

Survival rates were calculated on an actuarial basis by the method of Kaplan & Meier. Corrected survival rates are presented, in other words, patients who died due to tumor or treatment were counted as dead, while patients who died due to intercurrent diseases were counted as alive.

The logrank test was used to compare survival rates. The actuarial overall survival is given in parentheses. Of the 172 patients, 115 died with cancer, 13 of complications, 24 from intercurrent diseases, and 20 patients were still alive. The number of intercurrent deaths was much higher than was expected on the basis of age and sex specific death figures in the Dutch population: The expected number of deaths was 7.9. This means either that registration of cause of death was not reliable, or that the patient population apart from the esophageal malignancy constituted a high risk group (probably because of high consumption of alcohol and tobacco). We believe that the latter alternative is the most probable explanation.

Combined treatment with curative intention. This treatment started with preoperative roentgen irradiation from a 4 to 6 MeV linear accelerator by means of two parallel opposed portals to a total of 40 Gy in 20 fractions in 4 weeks. Field sizes extended to at least 5 cm from the upper and lower borders of the tumor and to about 3 to 4 cm from the lateral borders.

Table 1

Histology

Squamous cell carcinoma	110	
Proximal esophagus		17
Rest of esophagus		93
Adenocarcinoma	51	
In Barrett's esophagus		20
In 'normal' esophagus		31
Undifferentiated carcinoma	7	
Proximal esophagus		1
In Barrett's esophagus		1
Rest of esophagus		5
Small cell carcinoma	2	
Mucoepidermoid carcinoma	1	
Unknown	1	

Table 2

Actuarial survival rates corrected for intercurrent death and actuarial overall survival rates (in parentheses)

	No. of cases		Survival (per cent)	
			2 years	4 years
Curable–operable (n=91)				
Surgically resectable	69		48 (38)	39 (26)
Surgically unresectable	12		–	–
Refused surgery	10			
Curative radiation therapy		6	27 (17)	27 (17)
No further therapy		4	–	–
Inoperable (n=40)				
Curative radiation therapy	32		11 (6)	–
Palliative therapy	8		–	–
Radiation therapy		7		
Tube		1		
Incurable (n=41)			–	–
Palliative therapy				
Radiation therapy	37			
Tube	4			

Four weeks after irradiation the patient was re-evaluated with regard to any surgical contra-indications. If no contra-indications existed, surgery was performed in the 5th week. If curative resection was possible, resection of the involved part of the esophagus was carried out with inclusion of at least 5 cm of uninvolved esophagus proximal and distal to the tumor. If possible, the margins of resection were located outside the field of irradiation. Reconstruction was carried out by some form of gastric tube, gastric interposition, or interposition of the left colon, depending on the preference of the surgeon and the anatomic possibilities. If metastases were found during the operation or if the tumor was unresectable—this was the case in 12 patients (15%)—resection or a bypass was not done (Table 2).

If histologic examination of the surgical specimen revealed that the resection was not radical, postoperative

radiation therapy was given within 6 weeks of the operation. The irradiation was given with a 4 MeV roentgen beam to a tumor dose of 30 Gy in 15 fractions in 3 weeks; a rotation or 3-field technique was used.

For carcinomas in the postcricoid region and the upper esophageal sphincter area, radiation therapy was often preferred as the only modality, for the following reasons: The results of radiation therapy alone are in these regions better than in other esophageal sites (23, 24, 26), and surgical management of tumors in these areas involves extensive and mutilating intervention including both removal of the esophagus and part of the pharynx and sacrifice of the larynx. For tumors with this location the procedure started with radiation therapy: 40 Gy in 20 fractions in 4 weeks. After a 3-week interval esophagoscopy was repeated. If no significant tumor was found, radiation therapy was continued and 30 Gy given in 15 fractions in 3 weeks. If the tumor persisted, surgical intervention, with resection of larynx, pharynx, and part of the esophagus, was performed instead. Reconstruction was done with a free ileum interposition.

Of the 91 operable patients with theoretically curable disease, 69 had a resectable tumor and 12 an unresectable tumor while 10 patients refused surgery. Of the 69 patients with resectable tumor 46 received preoperative irradiation followed by surgery. Fifteen patients had preoperative irradiation, surgery and postoperative irradiation, due to local findings at the operation or to microscopic tumor in the margins. Eight patients had primary surgery and postoperative irradiation (5 were referred to the Group after resection elsewhere, 1 had a perforation after endoscopy, 1 had had earlier irradiation of the area, 1 had a proximal tumor with resection and a free ileum transplant).

In the 69 patients who completed the combined treatment the actuarial survival corrected for intercurrent death after 2 and 4 years was 48 per cent (38%) and 39 per cent (26%), respectively (Table 2).

The resectability rate was 85 per cent (69 out of 81) and the postoperative mortality rate was 20 per cent (13 out of 64). As regards the postoperative mortality, leakage of the anastomosis was the cause in 4 patients, sepsis in 2, mediastinitis in 1, cardiopulmonary complications in 5, and death at operation in 1 case.

Tumor size and sex are important prognostic factors. Tumor length estimated according to the number of corresponding underlying vertebrae was known in 158 of the 172 patients. Patients with a tumor length of less than two vertebrae had a significantly better survival than the other patients and the 4-year actuarial corrected survival was 30 per cent (14%) and 14 per cent (9%), respectively. In the 69 patients with combined treatment with curative intention the corresponding 4-year survival was 60 per cent (29%) and 30 per cent (23%), respectively in the two groups. Females showed a significantly better survival than males, even though female patients had relatively larger tumors than males. Among the 172 patients the 4-year actuarial corrected survival was 31 per cent (22%) in females and 12 per cent (7%) in males. In the combined treatment group the corresponding 4-year survival for females and males was 61 per cent (43%) and 29 per cent (18%) ($p=0.04$), respectively. Correction for tumor size did not essentially change the p-values. No significant influence on survival, from age, symptoms, or pathology was found in the analyses.

Radiation therapy with curative intention. In 32 patients, the tumor appeared to be curable but because of the poor general condition a thoraco-laparotomy could not be performed, and curative radiation therapy was therefore proposed. Six patients belonging to the operable-curable group who refused surgery after the 4-week interval were also included in this category.

The treatment was given in a split-course or in one course. With the split-course, 40 Gy was given in 20 fractions in 4 weeks, followed by a pause of 4 weeks, after which 26 to 30 Gy in 13 to 15 fractions in 2 ½ to 3 weeks was given. The first part was given using two parallel opposed portals and the second by rotation or 3-field technique. With the one course treatment, the total dose was 50 to 55 Gy in 20 to 22 fractions in 4 to 4 ½ weeks given by two parallel opposed fields or partly by a 3-field technique. The actuarial 4-year corrected survival for these 38 patients was 5 per cent (3%).

Palliative therapy. When the tumor was not theoretically curable, or when the patient was inoperable or due to the general condition not suitable for curative radiation therapy, other measures had to be taken in order to maintain or to improve food passage. These measures included palliative radiation therapy, insertion of a Celestin tube, application of a gastrostomy, or sometimes insertion of a gastric tube. With these measures it was practically always possible to prevent patients from spitting out their saliva or sputum constantly in the terminal phase. For long lasting palliation with radiation therapy a rather high dose was necessary, ranging from 30 Gy in 10 fractions in 10 days to 50 Gy in 20 fractions in 4 weeks.

Forty-four patients received such palliative radiation therapy. The 2-year survival was 0 per cent. The Celestin tube could be introduced during surgery or by endoscopy. In patients in whom metastases were found during surgery or in whom the tumor was unresectable, no resection or bypass was done. If the patient had severe dysphagia before surgery a Celestin tube was inserted at the operation. From 1977 on, the Celestin tube was inserted endoscopically in most of the patients according to the method of Atkinson.

Results and Discussion

The results of the combined treatment used by the Group were, in comparison with other reported series from the Western World, rather favorable (Table 3). Moreover, the results from the period 1978–1981 were

Table 3

Results of treatment of esophageal carcinoma in Rotterdam (RRTI/AZR-D) in comparison with results mentioned in the literature (survival after radiation therapy/resection)

	No. of cases		Resectable (per cent)	Operation mortality (per cent)	Survival (per cent)		
					2 years	4 years	5 years
NAKAYAMA et coll. (22)	119						
		55 surg.		5.4	21[a]		19[c]
		64 RT + surg.		4.4	35[b]		37.5[d]
AKAKURA et coll. (1)	346						
		229 surg.	39.7	13.2	20		13.6[e]
		117 RT + surg.	82.1	20.8	32		25[e]
MARKS et coll. (20)	137						
		101 RT + surg. resect.	74	18	22.8		13.9[f]
		36 RT + surg. explor.			–		–
WU & HUANG (30)	408						
		RT + surg.	81.9	3.9			31.6[g]
LAUNOIS et coll. (19)	109						
		47 surg.	70	23			11.5[h]
		62 RT + surg.	76	23			9.5[h]
RRTI/AZR-D VAN ANDEL et coll. (3)	133						
		RT + surg.	60.9	21			21[i]
RRTI/AZR-D Present series	81						
		RT + surg.	84	20	48	39[i]	
					38	(26)[j]	

[a] Reduced sample method (n=52).
[b] Reduced sample method (n=57).
[c] Reduced sample method (n=21).
[d] Reduced sample method (n=8).
[e] Method of calculation of survival rate not specified.
[f] Absolute survival rate.
[g] Reduced sample method (n=212).
[h] Actuarial survival rate.
[i] Actuarial survival rate corrected for intercurrent death.
[j] Actuarial overall survival rate.

better than the Group's own results from the years 1970–1977. In the 81 patients from the earlier period who completed the combined treatment the actuarial corrected 5-year survival was 21 per cent, and a significantly better survival for females than for males was found (42% versus 12%) (3). The difference between the two periods is not explained by the operation mortality, which was similar in both periods. The more favorable survival now observed can possibly be explained by a more restrictive selection of patients or by a changed referring pattern to our Group. Furthermore, it is quite possible that patients with carcinoma of the esophagus are nowadays diagnosed at an earlier stage.

A second striking difference between 1970–1977 and 1978–1981 was that the percentage of operable–curable patients in whom metastases or extension beyond the esophagus were found at operation diminished from 39 per cent to 15 per cent. EEFTINCK SCHATTENKERK et coll. (6) demonstrated that this decrease occurred already before the diagnostic work-up was enriched with CT and ultrasonography. From this it might be conjectured that the patients in the present series had less advanced disease.

A third favorable development occurring in 1983 and 1984 has been that the operation mortality rate has decreased to less than 10 per cent.

The proportion of adenocarcinoma located either in normal esophageal or in Barrett's epithelium was rather high in this series (30%). Despite the fact that some earlier reports (9) have given a worse prognosis for adenocarcinoma than for squamous cell carcinoma, this did not seem to influence the survival of our patients.

A comparison between the combined treatment group and the curative radiation therapy group with respect to the therapeutic results is not justified, because of selection factors. Only in a Chinese investigation have much better results been reported, but most of the patients had very early esophageal cancer discovered during a population survey (14). Advocates of combined treatment suggest that both resection and survival rates increase with this method without remarkable increase of the postoperative mortality (1, 2, 21, 22, 30). In 1979, WU & HUANG

proposed combination therapy for advanced lesions with dubious resectability (30). Among 408 patients irradiated preoperatively with 20 to 40 Gy in 2 to 4 weeks, 334 (=81.9%) were resectable. In their series 81.5 per cent of the tumors were larger than 5 cm and 70.2 per cent extended beyond the esophagus. The operative mortality was 3.9 per cent and the 5-year overall survival 31.6 per cent. They concluded: 'These figures speak rather favorably for the value of preoperative radiation therapy. We are of the opinion that this type of combined therapy is to be recommended for carcinoma of the esophagus of questionable resectability.'

Whether the combined treatment is superior to surgery alone is still a matter of discussion and can only be answered by randomized prospective studies. LAUNOIS et coll. did not find any advantage from preoperative irradiation, but their investigation has been criticized on the basis of the radiation treatment plan (19). The trial of the European Organization for Research on Treatment of Cancer (EORTC) does not, so far, show improvement in resectability or overall survival, with preoperative irradiation (8). A point for criticism regarding this trial is the time interval between irradiation and surgery, which has a maximum of 8 days, making an improvement of the resectability doubtful.

In conclusion, palliative treatment of carcinoma of the esophagus has markedly improved in the past decennium and the results of curative therapy seem to show an improvement for as yet undetermined reasons. The Group recommends that patients with esophageal carcinoma should be treated at centres where wide experience can be made available.

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REFERENCES

1. AKAKURA T., NAKAMURA Y., KAKEGAWA T., NAKAYAMA R., WATANABE H. and YAMASHITA H.: The combined treatment for surgery of carcinoma of the esophagus with pre-operative radiation. Chest 57 (1970), 47.
2. AKIYAMA H., TSURUMARU M. KAWAMURA T. and ONO Y.: Principles of surgical treatment for carcinoma of the esophagus. Analysis of lymph node involvement. Ann. Surg. 194 (1981), 438.
3. VAN ANDEL J. G., DEES J., DIJKHUIS C. M. et coll.: Carcinoma of the esophagus. Results of treatment. Ann. Surg. 190 (1979), 684.
4. CUCINGNAN R. A. and CAREY J. S.: Carcinoma of the esophagus (collective review). Ann. Thorac. Surg. 26 (1978), 274.
5. DIJKHUIS C. M.: The treatment of esophageal cancer. Thesis, University of Rotterdam, 1982.
6. EEFTINCK SCHATTENKERK M., OBERTOP H., MUD H. J. et coll.: Assessment of curative resectability and operative mortality of esophageal cancer. (In Dutch.) Nederlandse Vereniging voor Gastroenterologie, 1985 (Abstract).
7. ENCKE A., DIETZ R. and ULLRICH F.: Diagnosis and treatment of upper gastrointestinal tumors. *In:* Surgery of esophageal cancer. F8a-4409, p. 113. Excerpta Medica, Amsterdam 1981.
8. European Organization for Research on Treatment of Cancer, Gastointestinal Tract Cancer Cooperative Group. Preoperative Radiotherapy for Carcinoma of the Esophagus: Results of a Prospective Multicentric Study. *In:* Esophageal disorders. Pathophysiology and therapy, p. 367. Edited by T. R. DeMeester and D. B. Skinner. Raven Press, New York 1985.
9. FAINTUCH J., SHEPARD K. and LEVIN B.: Adenocarcinoma and other unusual variants of esophageal cancer. Sem. Oncol. 11 (1984), 196.
10. FLETCHER G. H.: Basic principles of the combination of irradiation and surgery. Int. J. Radiat. Oncol. Biol. Phys. 5 (1979), 2091.
11. — Subclinical disease. Cancer 53 (1984), 1274.
12. FRANKLIN R., STEIGER Z., VAISHAMPAYAN G. et coll.: Combined modality therapy for esophageal squamous cell carcinoma. Cancer 51 (1983), 1062.
13. FRASER R. W., WARA W. M., THOMAS A. N. et coll.: Combined treatment methods for carcinoma of the esophagus. Radiology 128 (1978), 461.
14. HUANG GUO JUN, SHAO LINGFANG, ZHANG DAWEI et coll.: Diagnosis and surgical treatment of early esophageal carcinoma. Chin. med. J. 94 (1981), 229.
15. KELSEN D. P., AHUJA R., HOPFAN S. et coll.: Combined modality therapy of esophageal carcinoma. Cancer 48 (1981), 31.
16. — BAINS M., HILARIS B. et coll.: Combination chemotherapy of esophageal carcinoma using Cis-platin, Vindesine and Bleomycin. Cancer 49 (1982), 1174.
17. — HILARIS B., COONLEY C. et coll.: Cis-platinum, Vindesine and Bleomycin chemotherapy of local-regional and advanced esophageal carcinoma. Amer. J. Med. 75 (1983), 645.
18. KOK T. C., OUWERDIJK R. J. TH., BOOT J., DEES J. and VAN BLANKENSTEIN M.: Palliative endoscopic intubation for malignant oesophago-gastric strictures. Analysis of four years therapy. (In English.) Autumn Report, Dutch Soc. of Gastro-Enterology, 1984 (in press).
19. LAUNOIS B., DELARUE D., CHAMPION J. P. and KERBAOL M.: Preoperative radiotherapy for carcinoma of the esophagus. Surg. Gynec. Obstet. 153 (1981), 690.
20. MARKS R. D., SCRUGGS H. J. and WALLACE K. M.: Preoperative radiation therapy for carcinoma of the esophagus. Cancer 38 (1976), 84.
21. NAKAYAMA K. and KINOSHITA Y.: Surgical treatment combined with preoperative concentrated irradiation. J. Amer. med. Ass. 227 (1974), 178.
22. — ORIHAIN H. and YAMAGUCHI K.: Surgical treatment combined with preoperative concentrated irradiation for esophageal cancer. Cancer 20 (1967), 778.
23. PEARSON J. G.: Carcinoma of the oesophagus. Operation or radiation. Langenbecks Arch. Chir. 337 (1974), 739.
24. — Carcinoma of the oesophagus. Value of radiation therapy. J. Amer. med. Ass. 227 (1974), 181.
25. ROBERTS J. G.: Cancer of the oesophagus. How should tumor biology affect treatment. Brit. J. Surg. 67 (1980), 791.
26. ROSS W. M.: Carcinoma of the oesophagus. Radiotherapy of carcinoma of the oesophagus. Proc. roy. Soc. Med. 67 (1974), 389.
27. SMITH F. S., GIBSON P. and NICHOLLS T. T.: Carcinoma of the esophagus. Preoperative irradiation followed by planned resection for lesions in the middle and lower thirds. An interim report. Aust. N.Z.J. Surg. 45 (1975), 176.
28. STEIGER Z., FRANKLIN R., WILSON R. F. et coll.: Eradication and palliation of squamous cell carcinoma of the esophagus

with chemotherapy, radiotherapy and surgical therapy. J. Thorac. Cardiovasc. Surg. 82 (1981), 713.
29. WANG C. C.: Biologic basis for combined radiation therapy and surgery. *In:* Radiation therapy for head and neck neoplasms. Chapter 3, p. 13. Edited by C. C. Wang. Wright, Boston 1983.
30. WU YING-K'AI and HUANG KUO-CHUN: Chinese experience in the surgical treatment of carcinoma of the esophagus. Ann. Surg. 190 (1979), 361.
31. XIAN ZHI GU: Radiotherapy for carcinoma of the esophagus. *In:* Carcinoma of the esophagus and gastric cardia, p. 258. Edited by Guo Jun Huang and Wu Ying K'ai. Springer Verlag, Berlin Heidelberg New York Tokyo 1984.