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Review article

Oesophageal squamous cell carcinoma: II. A critical review of radiotherapy*

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SUMMARY

There has been no controlled trial of radiotherapy versus surgery for squamous cell carcinoma of the oesophagus. Radiotherapy is generally used for those patients with extensive disease or those who are unfit for surgery. In spite of this, the 1-year survival of 18 per cent is similar to that for surgically treated patients and there is no equivalent operative mortality. The 5-year survival is 6 per cent compared with that for surgery of 4 per cent. There are no results available to suggest what would happen if a patient with a localized tumour, technically suitable for surgical resection, were treated instead by radiotherapy.

It is no surprise that radiotherapy has been used for squamous cell oesophageal carcinoma because squamous skin lesions respond so well. However, since the classic paper by Pearson in 1966 (1) from Edinburgh there has been no comparable study nor any subsequent controlled trial of the results of radiotherapy versus surgery. In the majority of articles patients have been selected on a very random basis, either being rejects from surgery or an incomplete selection from the community. The results are as difficult to assess as those for surgical treatment. No radiotherapist appears to have been given the opportunity to treat early cases of similar grading to those that do well after surgery. Nevertheless, an attempt will be made to give mean or average numbers based on the treatment of all possible patients in a given population avoiding bias and selection. The figures obtained from the literature during a 25-year period between 1954 and 1979, amounting to 8489 patients in 49 articles, are set out in *Table 1*. The even more controversial problem of the combination of radiotherapy with surgery has been omitted because of incomplete evidence.

Methodology

The usual type of radiotherapy is megavoltage. Kilovoltage is a thing of the past and neutron therapy is unlikely to be used in the future. The normal equipment is a linear accelerator, although some centres still use a cobalt source. Techniques offered are three fields, opposing fields, rotation and multiple fields. Nobody knows the optimum dosage, but the minimum dose for radical treatment is accepted as 5000 rad and the normally accepted maximum is 6000 rad, above which unacceptable side effects occur (51). A few centres use the higher dosage of 6800 rad (37, 52, 53). Of more importance than the total dose is the daily dose, which has a range between 175 and 500 rad per day, with a mean of 200 rad. Since the majority of the Western world takes two holidays a week, the average treatments are five per week; therefore the total length of radical treatment will never be shorter than 3 weeks and may have to extend to 8. Using a total between 5000 and 6000 rad there exists a great difference in the daily dose and length of treatment. There is no convincing evidence to show that changing any of these variables within limits affects the outcome. Nobody has asked the patient what the optimum span is for himself, but personal experience of patients undergoing radiotherapy is that after 4 weeks the patient's morale is low. If there is nothing to be gained, why spread out the treatment? Five thousand rad given over 4 weeks in 20 days of treatment at 250 rad each day would appear to be acceptable to most radiotherapists. No mention has been made of the biological effects of irradiation on the tumour because there are not enough details given in the papers reviewed. However, it is obviously most important, being related to the total dose, the number, size and frequency of treatments and the overall time for the course of radiotherapy.

Complications

The complications of radiotherapy are mainly those of morbidity rather than mortality. One reason for the lack of mortality may be that radiotherapy is stopped if the patient becomes too ill. In Finland this occurs in 10 per cent of cases (54). Semantics may also play their part since if radical radiotherapy treatment is started, this converts to palliative if the patient becomes unfit to complete the course of treatment. Using a neat syllogism the majority of complications can then be transferred under the heading of palliation. The true complications or morbidity of radiotherapy include skin burns, leucopenia, pulmonary fibrosis and spinal cord lesions leading to paraplegia. In a modern unit using properly planned radiotherapy none of these should occur.

* Part I of this paper, 'A critical review of surgery', appeared in the June issue.

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Table I: DATA FROM 49 PAPERS ON OESOPHAGEAL CANCER RADIOTHERAPY (8489 PATIENTS)

First author	Ref.	Year	Country	Patients	% pall. RT	Survival (%) 1 yr	2 yr	5 yr
Appelquist	(2)	1972	Finland	188	31			3
Buschke	(3)	1954	USA	60	22	33	12	4
Cederquist	(4)	1978	Denmark	700	45			4
Cossu	(5)	1967	Italy	154		16	8	2
Eberhardt	(6)	1970	Germany	41				5
Eichhorn	(7)	1966	Germany	872				4
Gary-Bobo	(8)	1978	France	530		14	4	2
Gunderson	(9)	1976	USA	169				19
Gynning	(10)	1965	Sweden	355	22	25		6
Hankins	(11)	1972	USA	181	34			1
Heinze	(12)	1973	Germany	110		14		2
Holsti	(13)	1969	Finland	132		31	18	
Humphrey	(14)	1968	USA	188		18		1
Krishnamurthi	(15)	1965	India	100	22	12	5	4
Kuttig	(16)	1966	Germany	27				7
Lawler	(17)	1969	USA	68	93			1
Lawrence	(18)	1976	USA	169				19
LeBorgne	(19)	1963	Uruguay	294				3
Lederman	(20)	1966	England	196		19	7	1
Leon	(21)	1971	USA	196				1
Levit	(22)	1970	USA	25		12		
Lewinsky	(23)	1975	USA	85				0
Lowe	(24)	1972	USA	224		11		3
Marcial	(25)	1966	Puerto Rico	197	23	28		4
Marks	(26)	1976	USA	82	60		6	2
Martinez	(27)	1964	Puerto Rico	362		8	4	1
Meynard	(28)	1965	France	110		16	5	1
Millburn	(29)	1968	USA	64	61			9
Miller	(30)	1962	England	33	76			
Moor	(31)	1968	S. Africa	17	100			
Moseley	(32)	1968	USA	26	100			4
Mustard	(33)	1956	Canada	125		18	8	1
Nakayama	(34)	1967	Japan	100				6
Pearson	(35)	1978	Scotland	288	83		27	20
Pelletier	(36)	1972	Canada	21		10	5	
Pierquin	(37)	1966	France	115				3
Robertson	(38)	1967	Canada	39				8
Ross	(39)	1974	England	40				13
Skinner	(40)	1976	USA	21		18		
Stoller	(41)	1977	Canada	53		8	4	
Takita	(42)	1977	USA	57				2
Vanhoutte	(43)	1977	Belgium	120	28	22	6	2
Verhaeghe	(44)	1971	France	300	30	21	4	
Voutilainen	(45)	1967	Finland	140		28	12	7
Wahlers	(46)	1975	Germany	205	39	21	3	2
Walker	(47)	1964	USA	35				6
Wara	(48)	1976	USA	129		18	6	1
Watson	(49)	1963	Canada	19	54			21
Watson	(50)	1960	USA	727				1

% palliative radiotherapy 51 ± 28 (mean ± 1 s.d.)
% 1-year survival 18 ± 7 (mean ± 1 s.d.)
% 2-year survival 8 ± 6 (mean ± 1 s.d.)
% 5-year survival 6 ± 6 (mean ± 1 s.d.)

Tracheo-oesophageal fistula or aorto-oesophageal fistula should truly be considered complications of the disease process itself; the radiotherapy destroys the cancer cells already extending into the trachea or the aorta and merely precipitates what is inevitable. This raises the question as to whether radiotherapy should be advised when the tumour has infiltrated so far, and this will be discussed under contraindications. Dysphagia may get worse at any time during radiotherapy, with a peak at 5 days (35), but also in the few weeks after the treatment has finished or at any subsequent time. It is always difficult to assess why this occurs and whether it will inevitably happen. The majority of patients gradually lose their dysphagia during treatment and then continue to improve; however, up to 50 per cent may need oesophageal dilatation (35). Those with proliferative tumours, even though they may be circumferential, usually have necrosis of the tumour with radiotherapy and improve rapidly. Those with ulcerated tumours occupying only part of the wall may suffer oedema and temporarily increased difficulty. In practice, however, it is impossible to decide which tumours will get worse before they get better. Fibrous strictures are probably not seen for at least 3 months. Re-epithelization of the oesophagus can take up to a year or more and may never occur even without there being any dysphagia. The fibrous strictures can develop with or without the epithelium having regenerated. Local recurrence after

adequate radical treatment rarely occurs (54). There is one study of preoperative radiotherapy, using 5000 rad 2–4 weeks before surgical resection (55), which showed histological evidence of residual tumour cells at this stage, so it is clear that the majority of epithelial cancer cells take a few weeks to die and the process continues after the treatment has finished. The main effect is to prevent the growth of the next generation of cells after mitosis.

Survival

It is difficult to be accurate about these figures because they involve more patient selection and bias than those for surgery, and because the majority of patients had been referred by surgeons as unfit for operation. The mean figure for 1-year survival is 18 per cent, 2-year 8 per cent and 5-year 6 per cent. However, in the only three papers (1, 3, 46) out of the total of 49 where the original population could be compared to that of the surgical series the figures respectively were 42, 46 and 44 per cent for 1-year survival, 8, 15 and 27 per cent for 2-year and 6, 6 and 20 per cent for 5-year. There is no study available to show what the results would be if the most favourable tumours for surgery were actually treated by radiotherapy instead of operation.

Quality of life

The majority of patients will have their dysphagia relieved after radical radiotherapy. They will certainly be able to swallow liquids and their saliva, which is often more difficult than clear fluid, but it is wrong to suggest that they will have no difficulty. There is often some dysphagia with fresh bread and solid meat, even if well chewed. If patients can eat minced and mashed food they should be able to sit down to a meal with their families. When they can swallow this consistency and have good teeth which they are prepared to use, they should actually be able to eat normal food. The fact that the average time interval with dysphagia symptoms before diagnosis is over 6 months (1, 56, 57) implies that some of these patients are uninterested in gastronomy, have a high threshold for abnormal swallowing and are not worried about this degree of dysphagia. It is unwise either to dilate or insert a tube into an oesophageal carcinoma before or during radiotherapy because the resultant oedema may increase dysphagia and the tube will fall through later as the tumour regresses. The majority of patients can manage clear liquids and, with the development of Aminutrin, Vivonex and Clinifeed, an adequate calorie intake can be achieved either by drinking or infusion through a 1 mm bore polyvinyl tube. There is usually no justification for a nasogastric tube with its wider bore and greater discomfort, and there should be no need for parenteral nutrition which requires intravenous lines, is expensive and not devoid of complications. Management of subsequent dysphagia is essentially similar to that of a benign stricture, using dilatation to at least 30 FG (10 mm in diameter). Some strictures can be dilated to 60 FG. Only if the dilatations are unsuccessful because they have to be done too frequently is there any need for the insertion of tubes of the Souttar or Celestin types, but many patients never need any dilatation at all. Detailed figures are rarely given as to how frequently a patient needs dilatation and whether it is dependent on the original tumour itself or the type of radiation. The reason for this must lie in the lack of interest radiotherapists have for mechanical obstructions (very few of the articles written by radiotherapists have a friendly surgeon or gastroenterologist involved). So, if one of the main criticisms of radiotherapy is that the patients may require subsequent bouginage, this must not be considered an unsurmountable problem since it can be dealt with by a specialist. After surgery 30 per cent of the patients need oesophageal dilatation (58) and this should be compared with an estimated 50 per cent after radiotherapy (35).

Palliative radiotherapy or none at all?

The difference between radical radiotherapy and palliative radiotherapy is difficult to judge. One definition is based on the fact that all patients are submitted to radical treatment and, if they cannot complete, are then put into the palliative group. The words curative radiotherapy are not truly applicable when the 5-year survival rate is 6 per cent. The problem arises, however, as to whether all patients with oesophageal squamous cell carcinoma should be subjected to a radical course of radiotherapy. Obviously if there is a tracheo-oesophageal fistula, present in 6–12 per cent (48, 57, 60), radiotherapy will not help either the symptom of continuous coughing nor the inevitable process of the disease. This is an extreme example, but the problem arises as to whether radical radiotherapy is contraindicated when the tumour is extensive. Only 58 per cent of patients with oesophageal carcinoma are operable and 39 per cent resectable, leaving 61 per cent without definitive surgical treatment and the question is whether radiotherapy should be given in anything other than palliative doses to those patients with extensive tumours, with nodes involved far away from the tumour or with distant metastases. Contraindications to radiotherapy are discussed by only a few authors (15, 25, 52, 58). These include age or infirmity, fistulas and distant metastases. Some authors include pain as an indication for symptomatic treatment (59) but others exclude it because it may indicate mediastinal spread with no possibility for radical treatment (48). Only a minority of radiotherapy authors consider that indications should be very exact, avoiding long tumours and those that might have spread through the adventitia.

There are no papers from which one can obtain sufficient data, but it appears that the majority of patients, like those undergoing surgical treatment, have extensive disease whose natural history cannot be changed by radiotherapy. Symptomatic therapy is then indicated, and if dysphagia or pain cannot be improved by radiotherapy, there would seem no point in using it. There can be no justification for the indiscriminate use of radiotherapy.

Conclusion

The facts are incomplete with regard to radiotherapy. The bias of patient selection is even greater than with surgery. Many patients are submitted for radiotherapy having been rejected for an operation, usually because of extensive disease. There is no epidemiological study of radiotherapy used on all patients in a community. There has never been a controlled trial of surgery versus radical radiotherapy. There has never been a comparison of operative resection versus radiotherapy for those particular tumours which are well treated by both methods, namely the short tumours less than 5 cm long with localized disease. In both surgical and radiotherapy studies the same problem arises, namely the

management of patients with extensive disease unsuitable for radical treatment who account for at least 50 per cent of all patients with the condition, and in these patients symptomatic relief of pain and mechanical obstruction by other methods is most important.

Answers are required to three main questions. Are the good results of both radiotherapy and surgery entirely due to the limited extent of that particular original tumour and unrelated to treatment? If radiotherapy was used in patients with less extensive disease rather than those rejected by surgeons, would the results improve dramatically? If the extent of the tumour could be assessed, staged and made equal for true comparison, is radiotherapy better than surgery for improving the quality and quantity of the remaining years?

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