3. **Oesophageal Cancer**

Introduction

Oesophageal cancer is a relative uncommon cancer in Sweden, compared to many other countries in the world. In 2000, 261 men and 117 women were diagnosed with oesophageal cancer in a population of 8.7 million, which gives an incidence of 6.0/100 000 for male cancer and 2.6/100 000 for female cancer, compared to 3.2 and 1.1 respectively in World Standard Rate per 100 000.The median age at diagnosis in Sweden is 72. The cancer is associated with spicy food, alcoholic beverage consumption, chronic inflammations and cigarette smoking. Diets high in fresh fruits and vegetables are consistently associated with reduced risks.

There are large geographical differences in incidence. The highest incidence rate is among women in northern Iran, while the lowest incidence is found among Mormon women in the US. The disease is also common in the Lin Xian valley in eastern China, due to lack of important minerals in the earth combined with a high intake of a highly suspicious fungus. In Soweto, South Africa, the disease is nearly epidemic with an incidence of 125 per 100 000 males, linked to high intake of maize beer. Also in northwestern France there is a high incidence of this cancer and heavy cigarette smoking combined with large intake of calvados are considered to be the risk factors.

Oesophageal cancer is most often located in the lower two thirds of the oesophagus. Squamous cell carcinoma is the most common histology and represents about 85 per cent of the cases. The other 15 per cent include adenocarcinoma and some small groups of oat cell carcinoma. In some publications, during the last 10–15 years from the US, there are an increasing proportion of adenocarcinomas, now comprising up to 50 per cent of many series. There is a big racial discrepancy in that the rate of squamous cell carcinoma is six times higher among black than white males, while adenocarcinomas occur at a frequency three times greater in whites. This makes squamous cell oesophageal cancer one of the most common

malignancies among black men in the US. No such change in relations between the different types of histology has been noticed in Sweden.

The staging is based on the TNM-classification.

Surgery is the primary treatment in small, early stages (T1–2 NX M0) of oesophageal cancer. For more advanced but still localized disease, radiotherapy alone or in combination with surgery has been used extensively, both for curative and palliative treatment. For inoperable patients the treatment has been radiotherapy and lately radiotherapy with concomitant chemotherapy. As palliative treatments intubation, hyperthermia and laser are also used, alone or in combination with intraluminal or external beam radiotherapy. The probability of surviving oesophageal cancer is low, with typically less than 10 per cent of patients surviving five or more years (median survival in the US, nine months), with similar rates of survival from squamous cell carcinomas and adenocarcinomas.

Search methods and selections

Computerized literature searches were performed in Medline from 1966 until October 2001. The MeSH search term oesophageal neoplasms was used in combination with radiotherapy as a subheading, MeSH-term and textword. Limitations to the following study designs were made: randomized controlled studies and meta-analysis. A supplementary search was made in Cochrane Library. All publications were reviewed by two referees, Maria Albertsson, oncologist and Johannes Järhult, surgeon.

Primarily 110 articles concerning oesophageal cancer were received. After exclusion of all non-English language papers, 88 remained. Two Cochrane Reviews (one identical with a meta-analysis of preoperative radiotherapy) were added (see reference list).

Reasons for exclusion of 45 abstracts and publications not selected for further analysis were:

Group		
A	9	not randomized studies
B	4	short comments/editorials/letters
C	1	basic science investigation
D	20	randomized studies, though not for radiotherapy (immunotherapy, hyperthermia, chemotherapy, analgesics, stents, laser and different surgical approaches)
E	2	uses of heavy charged particles
F	9	general topics not relevant to the aim of this study

Overview of studies

Resectable oesophageal cancer

Overview 1. Preoperative radiotherapy (1a) or preoperative chemo-radiotherapy (1b), (after the list of references).

The value of preoperative radiotherapy of potentially resectable oesophageal cancers is investigated in five randomized trials, two reasonably large with more than 100 patients in each treatment group. A meta-analysis including these five trials on preoperative radiotherapy was performed in 1998. The value of preoperative chemo-radiotherapy has been studied in five randomized trials. Only one with more than hundred patients in each group. In many of the preoperative radiotherapy trials the fractionation schedules are unconventional. The radiotherapy is either given to a very low total dose [8,27], or with very high dose per fraction [10,14, 26,39] or poorly reported [26,41].

The literature shows:

- There is no evidence that preoperative radiotherapy improves the survival of patients with potentially resectable oesophageal cancer. The results reported on preoperative chemo-radiotherapy are conflicting. Two small studies show improved survival with preoperative chemo-radiotherapy in patients with potentially resectable oesophageal cancer.

Resectable oesophageal cancer

Overview 2. Surgery alone versus surgery + postoperative radiotherapy (after the list of references).

Postoperative radiotherapy was evaluated in four randomized trials, three of which small with less than 50 patients in each treatment group. In the only reasonably large study, the radiotherapy was allowed to start as late as three months after surgery [37]. In two other studies ulceration, bleeding and fibrosis in the oesophageal substitute was reported to be the reason for worse quality of life and prognosis in the irradiated patients [13,43].

The literature shows:

- No survival benefit of postoperative radiotherapy in four randomized trials. In two of them superior survival in the surgery alone group.

Resectable oesophageal cancer

Overview 3. Comparison between surgery and radiotherapy and between different pre- and postoperative treatments (after the list of references).

In one trial better survival was reported with postoperative radiotherapy compared with the combination of pre- + postoperative radiotherapy [20]. Good overall survival in a Japanese trial comparing postoperative radiotherapy with postoperative chemotherapy, but no difference between the arms [1]. In one trial the value of intraoperative radiotherapy in combination with postoperative radiotherapy was investigated. The intraoperative radiation dose should be less than 25 Gy, to avoid fatal tracheal ulcerations. Preoperative hyperthermia in combination with chemo-radiotherapy in resectable oesophageal cancer seems to improve both local control and survival compared with preoperative chemo-radiotherapy alone [22].

The literature shows:

- The intraoperative radiation dose should be less than 25 Gy, to avoid fatal side-effects.
- Hyperthermia in combination with preoperative chemo-radiotherapy might improve both local control and survival in resectable oesophageal cancer.

Inoperable oesophageal cancer (surgically unresectable or medically inoperable patients).

Overview 4. Radiotherapy versus chemo-radiotherapy (after the list of references).

The rationales for combining radiotherapy and chemotherapy are to sensitize tumour tissue more than normal tissue to radiation and/or eradicating subclinical distant metastases. The combination can be either sequential (neoadjuvant or adjuvant) or concomitant. The Cochrane meta-analysis [43] comprises thirteen randomized trials, eight concomitant and five sequential [5,6,11,12,15,30,34]. The meta-analysis also included four Japanese or Chinese publications, one abstract and one article (randomization +/– chemotherapy) not indexed in Medline or CancerLit, not evaluated in the present overview. The meta-analysis demonstrates a 9 per cent mortality reduction at one and two years with concomitant chemo-radiotherapy, compared with radiotherapy alone, although some studies employed a lower total radiation dose in the combined treatment arm. No such benefit was observed with sequential treatment.

The literature shows:

- Concomitant chemo-radiotherapy gives in three out of eight randomized studies and in a meta-analysis significantly better survival rate than radiotherapy alone in inoperable oesophageal cancer.
- Sequential chemo-radiotherapy does not result in improved survival compared to radiotherapy alone in inoperable oesophageal cancer.

Inoperable oesophageal cancer (surgically unresectable or medically inoperable patients)

Overview 5. Different radiation doses and fractionation schedules (after the list of references).

In two trials the value of hyperfractionated radiotherapy was tested [33,40]. In the first a significantly better local control and survival rate was registered with hyperfractionation to the price of more acute radiation-induced side-effects. In the second trial a low total dose in the hyperfractionated group was used and no benefit was shown. In a Japanese

study boost with intraluminal brachytherapy gave statistically significant better survival rate compared with an external radiation boost [29].

The literature shows:

- Accelerated hyperfractionated radiotherapy might be superior to conventional radiotherapy.
- Brachytherapy seems to be superior to external radiotherapy for patients with small tumours.

Inoperable oesophageal cancer (surgically unresectable or medically inoperable patients)

Overview 6. Miscellaneous treatments (after the list of references).

For palliation, intubation and laser-treatment are used either alone or in combination with intraluminal brachytherapy or external beam radiotherapy with good effect on swallowing, but with no significant impact on survival.

The literature shows:

- Short survival in advanced cases after intubation. No improvement with the combination of either radiotherapy or chemotherapy.
- Significant better response rate and survival with chemo-radiotherapy compared to chemotherapy alone for patients with inoperable cancers.

Literature

The articles on which the conclusions in this report were based were classified and graded as follows (number of studies/number of patients).

	1 = High	2 = Moderate	3 = Low	Total
M	2/(2 369)*	–	–	2
C	9/1 617	17/2 358	16/1 797	42/5 772
Total	**11/1 617**	**17/2 358**	**16/1 797**	**44/5 772**

* The number of patients in the meta-analysis (M) is larger than the number in randomized studies (C) as one of the meta-analysis also included four Chinese and Japanese publications, not evaluated in the present overview.

Conclusions and comments

This overview of the literature on radiotherapy for oesophageal cancer is based on 44 publications including two meta-analysis and 42 prospective randomized trials. The following main conclusions can be drawn:

- There is a fairly strong evidence that preoperative radiotherapy does not improve the survival in patients with potentially resectable oesophageal cancer. (*Pro:* [8]M1, [14]C1, [7]C2; *con:* [28]C1).
- There is moderate evidence that preoperative chemo-radiotherapy has no beneficial impact on the survival of patients with potentially resectable oesophageal cancer. (*Pro:* [28]C1, [10]C2, [27]C2, [38]C2; *con:* [39]C2).
- There is no scientific evidence that postoperative radiotherapy does improve the survival in patients with resectable oesophageal cancer. The documentation is however poor, consisting of only three randomized trials. (*Pro:* [37]C2, [44]C2, [13]C3).
- There is a fairly strong evidence that concomitant (but not sequential) chemo-radiotherapy gives significantly better survival rate than radiotherapy alone in inoperable oesophageal cancer. The results of the reported clinical trials are however conflicting, and no solid conclusion can be drawn. (*Pro:* [43]M1, [11]C1, [16]C1, [19]C3; *con:* [5]C1, [30]C1, [34]C2, [35]C3, [12]C2, [4]C3, [6]C2).
- Hyperfractionated radiotherapy has been compared with conventionally fractionated radiotherapy in two randomized studies with conflicting results and no firm conclusion can be drawn. (*Pro:* [33]C1; *con:* [40]C3).

References

1. A comparison of chemotherapy and radiotherapy as adjuvant treatment to surgery for esophageal carcinoma. Japanese Esophageal Oncology Group. Chest. 1993;104:203-7. (C2)

2. Alberts AS, Anderson JD, Goedhals L, Cronje JD, Doman MJ. [Palliative radiation schedules with and without chemotherapy in advanced carcinoma of the esophagus]. S Afr Med J. 1984;66:289-91. (C3)

3. Alberts AS, Burger W, Greeff F, Schoeman L, Friediger D, Nel J, et al. Severe complications of 5-fluorouracil and cisplatin with concomitant radiotherapy in inoperable non-metastatic squamous cell oesophageal cancer after intubation – early termination of a prospective randomized trial. Eur J Cancer. 1992;28A:1005-6. (C3)

4. al-Sarraf M, Martz K, Herskovic A, Leichman L, Brindle JS, Vaitkevicius VK, et al. Progress report of combined chemoradiotherapy versus radiotherapy alone in patients with esophageal cancer: an intergroup study. J Clin Oncol. 1997;15: 277-84. (C2)

5. Andersen AP, Berdal P, Edsmyr F, Hagen S, Hatlevoll R, Nygaard K, et al. Irradiation, chemotherapy and surgery in esophageal cancer: a randomized clinical study. The first Scandinavian trial in esophageal cancer. Radiother Oncol. 1984;2: 179-88. (C1)

6. Araujo CM, Souhami L, Gil RA, Carvalho R, Garcia JA, Froimtchuk MJ, et al. A randomized trial comparing radiation therapy versus concomitant radiation therapy and chemotherapy in carcinoma of the thoracic esophagus. Cancer. 1991;67: 2258-61. (C2)

7. Arnott SJ, Duncan W, Gignoux M, Girling DJ, Hansen HS, Launois B, et al. Preoperative radiotherapy in esophageal carcinoma: a meta-analysis using individual patient data (Oesophageal Cancer Collaborative Group). Int J Radiat Oncol Biol Phys. 1998;41:579-83. (M1)

8. Arnott SJ, Duncan W, Kerr GR, Walbaum PR, Cameron E, Jack WJ, Mackillop WJ. Low dose preoperative radiotherapy for carcinoma of the oesophagus: results of a randomized clinical trial. Radiother Oncol. 1992;24:108-13. (C2)

9. Badwe RA, Sharma V, Bhansali MS, Dinshaw KA, Patil PK, Dalvi N, et al. The quality of swallowing for patients with operable esophageal carcinoma: a randomized trial comparing surgery with radiotherapy. Cancer. 1999;85:763-8. (C2)

10. Bosset JF, Gignoux M, Triboulet JP, Tiret E, Mantion G, Elias D, et al. Chemoradiotherapy followed by surgery compared with surgery alone in squamous-cell cancer of the esophagus. N Engl J Med. 1997; 337:161-7. (C2)

11. Cooper JS, Guo MD, Herskovic A, Macdonald JS, Martenson JA, Jr, Al-Sarraf M, et al. Chemoradiotherapy of locally advanced esophageal cancer: long-term follow-up of a prospective randomized trial (RTOG 85-01). Radiation Therapy Oncology Group. Jama. 1999;281: 1623-7. (C1)

12. Earle JD, Gelber RD, Moertel CG, Hahn RG. A controlled evaluation of combined radiation and bleomycin therapy for squamous cell carcinoma of the esophagus. Int J Radiat Oncol Biol Phys. 1980; 6:821-6. (C2)

13. Fok M, Sham JS, Choy D, Cheng SW, Wong J. Postoperative radiotherapy for carcinoma of the esophagus: a prospective, randomized controlled study. Surgery. 1993;113:138-47. (C3)

14. Gignoux M, Roussel A, Paillot B, Gillet M, Schlag P, Dalesio O, et al. The value of preoperative radiotherapy in esophageal cancer: results of a study by the EORTC. Recent Results Cancer Res. 1988;110:1-13. (C1)

15. Hatlevoll R, Hagen S, Hansen HS, Hultborn R, Jakobsen A, Mantyla M, et al. Bleomycin/cis-platin as neoadjuvant chemotherapy before radical radiotherapy in localized, inoperable carcinoma of the esophagus. A prospective randomized multicentre study: the second Scandinavian trial in esophageal cancer. Radiother Oncol. 1992;24: 114-6. (C2)

16. Herskovic A, Martz K, al-Sarraf M, Leichman L, Brindle J, Vaitkevicius V, et al. Combined chemotherapy and radiotherapy compared with radiotherapy alone in patients with cancer of the esophagus. N Engl J Med. 1992;326:1593-8. (C1)

17. Holsti LR. Clinical experience with split-course radiotherapy. A randomized clinical trial. Radiology. 1969;92:591-6 passim. (C3)

18. Hosokawa M, Shirato H, Ohara M, Kagei K, Hashimoto S, Nishino S, et al. Intraoperative radiation therapy to the upper mediastinum and nerve-sparing three-field lymphadenectomy followed by external beam radiotherapy for patients with thoracic esophageal carcinoma. Cancer. 1999;86:6-13. (C3)

19. Hukku S, Fernandes P, Vasishta S, Sharma VK. Radiation therapy alone and in combination with bleomycin and 5-fluorouracil in advanced carcinoma esophagus. Indian J Cancer. 1989;26:131-6. (C3)

20. Iizuka T, Ide H, Kakegawa T, Sasaki K, Takagi I, Ando N, et al. Preoperative radioactive therapy for esophageal carcinoma. Randomized evaluation trial in eight institutions. Chest. 1988;93:1054-8. (C2)

21. Kelsen DP, Minsky B, Smith M, Beitler J, Niedzwiecki D, Chapman D, et al. Preoperative therapy for esophageal cancer: a randomized comparison of chemotherapy versus radiation therapy. J Clin Oncol. 1990;8:1352-61. (C3)

22. Kitamura K, Kuwano H, Watanabe M, Nozoe T, Yasuda M, Sumiyoshi K, et al. Prospective randomized study of hyperthermia combined with chemoradiotherapy for esophageal carcinoma. J Surg Oncol. 1995; 60:55-8. (C2)

23. Kolaric K, Maricic Z, Roth A, Dujmovic I. Adriamycin alone and in combination with radiotherapy in the treatment of inoperable esophageal cancer. Tumori. 1977;63:485-91. (C3)

24. Kolaric K, Maricic Z, Roth A, Dujmovic I. Chemotherapy versus chemoradiotherapy in inoperable esophageal cancer. Results of three controlled studies. Oncology. 1980;37 Suppl 1:77-82. (C3)

25. Kolaric K, Maricic Z, Roth A, Dujmovic I. Combination of bleomycin and adriamycin with and without radiation on the treatment of inoperable esophageal cancer. A randomized study. Cancer. 1980; 45:2265-73. (C3)

26. Launois B, Delarue D, Campion JP, Kerbaol M. Preoperative radiotherapy for carcinoma of the esophagus. Surg Gynecol Obstet. 1981;153:690-2. (C3)

27. Le Prise E, Etienne PL, Meunier B, Maddern G, Ben Hassel M, Gedouin D, et al. A randomized study of chemotherapy, radiation therapy, and surgery versus surgery for localized squamous cell carcinoma of the esophagus. Cancer. 1994;73:1779-84. (C2)

28. Nygaard K, Hagen S, Hansen HS, Hatlevoll R, Hultborn R, Jakobsen A, et al. Pre-operative radiotherapy prolongs survival in operable esophageal carcinoma: a randomized, multicenter study of pre-operative radiotherapy and chemotherapy. The second Scandinavian trial in esophageal cancer. World J Surg. 1992;16:1104-9; discussion 10. (C1)

29. Okawa T, Dokiya T, Nishio M, Hishikawa Y, Morita K. Multi-institutional randomized trial of external radiotherapy with and without intraluminal brachytherapy for esophageal cancer in Japan. Japanese Society of Therapeutic Radiology and Oncology (JASTRO) Study Group. Int J Radiat Oncol Biol Phys. 1999;45:623-8. (C2)

30. Roussel A, Bleiberg H, Dalesio O, Jacob JH, Haegele P, Jung GM, et al. Palliative therapy of inoperable oesophageal carcinoma with radiotherapy and methotrexate: final results of a controlled clinical trial. Int J Radiat Oncol Biol Phys. 1989; 16:67-72. (C1)

31. Sargeant IR, Tobias JS, Blackman G, Thorpe S, Glover JR, Bown SG. Radiotherapy enhances laser palliation of malignant dysphagia: a randomized study. Gut. 1997;40:362-9. (C3)

32. Schmid EU, Alberts AS, Greeff F, Terblanche AP, Schoeman L, Burger W, et al. The value of radiotherapy or chemotherapy after intubation for advanced esophageal carcinoma– a prospective randomized trial. Radiother Oncol. 1993;28:27-30. (C3)

33. Shi XH, Yao W, Liu T. Late course accelerated fractionation in radiotherapy of esophageal carcinoma. Radiother Oncol. 1999;51:21-6. (C1)

34. Slabber CF, Nel JS, Schoeman L, Burger W, Falkson G, Falkson CI. A randomized study of radiotherapy alone versus radiotherapy plus 5-fluorouracil and platinum in patients with inoperable, locally advanced squamous cancer of the esophagus. Am J Clin Oncol. 1998;21:462-5. (C2)

35. Smith TJ, Ryan LM, Douglass HO, Jr, Haller DG, Dayal Y, Kirkwood J, et al. Combined chemoradiotherapy vs. radiotherapy alone for early stage squamous cell carcinoma of the esophagus: a study of the Eastern Cooperative Oncology Group. Int J Radiat Oncol Biol Phys. 1998;42: 269-76. (C3)

36. Sur RK, Donde B, Levin VC, Mannell A. Fractionated high dose rate intraluminal brachytherapy in palliation of advanced esophageal cancer. Int J Radiat Oncol Biol Phys. 1998;40:447-53. (C2)

37. Teniere P, Hay JM, Fingerhut A, Fagniez PL. Postoperative radiation therapy does not increase survival after curative resection for squamous cell carcinoma of the middle and lower esophagus as shown by a multicenter controlled trial. French University Association for Surgical Research. Surg Gynecol Obstet. 1991;173:123-30. (C2)

38. Urba SG, Orringer MB, Turrisi A, Iannettoni M, Forastiere A, Strawderman M. Randomized trial of preoperative chemoradiation versus surgery alone in patients with locoregional esophageal carcinoma. J Clin Oncol. 2001;19:305-13. (C2)

39. Walsh TN, Noonan N, Hollywood D, Kelly A, Keeling N, Hennessy TP. A com-

parison of multimodal therapy and surgery for esophageal adenocarcinoma. N Engl J Med. 1996;335:462-7. (C2)

40. Wan J, Guo BZ, Gao SZ. Accelerated hyperfractionation radiotherapy in esophageal cancer. An analysis of 172 cases. Chin Med J (Engl). 1991;104:228-9. (C3)

41. Wang M, Gu XZ, Yin WB, Huang GJ, Wang LJ, Zhang DW. Randomized clinical trial on the combination of preoperative irradiation and surgery in the treatment of esophageal carcinoma: report on 206 patients. Int J Radiat Oncol Biol Phys. 1989;16: 325-7. (C3)

42. Wobbes T, Baron B, Paillot B, Jacob JH, Haegele P, Gignoux M, et al. Prospective randomized study of split-course radiotherapy versus cisplatin plus split-course radiotherapy in inoperable squamous cell carcinoma of the oesophagus. Eur J Cancer. 2001;37: 470-7. (C1)

43. Wong R, Malthaner R. Combined chemotherapy and radiotherapy (without surgery) compared with radiotherapy alone in localized carcinoma of the esophagus (Cochrane Review). The Cochrane Library. 2001;(M1)

44. Zieren HU, Muller JM, Jacobi CA, Pichlmaier H, Muller RP, Staar S. Adjuvant postoperative radiation therapy after curative resection of squamous cell carcinoma of the thoracic esophagus: a prospective randomized study. World J Surg. 1995;19:444-9. (C2)

Overview 1a *Resectable oesophageal cancer.*
Preoperative radiotherapy + surgery versus surgery alone.

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Arnott 1998 [7] M	**A:** surgery **B:** preop RT + surgery	1 147 pts
Arnott 1992 [8] C included in meta-analysis [7]	**A:** surgery **B:** RT 2 Gy/fr to 20 Gy + surgery	176 potentially operable pts with SCC or ADC of the middle or lower thirds A 86 pts B 90 pts
Launois 1981 [26] C included in meta-analysis [7]	**A:** surgery **B:** RT 5Gy/fr to 40 Gy + surgery	1973–1976 124 pts with SCC A 57 pts B 67 pts
Wang 1989 [41] C included in meta-analysis [7]	**A:** surgery **B:** RT to 40Gy + surgery	1977–1985 206 pts A 102 pts B 104 pts
Gignoux EORTC 1988 [14] C included in meta-analysis [7]	**A:** surgery **B:** RT 3.3 Gy/fr to 33 Gy + surgery	1976–1982 208/229 pts eligible with potentially resectable SCC A 106 pts B 102 pts
Nygaard 2nd Scand trial 1992 [28] C Included in meta-analysis [7], (only groups A and C)	**A:** surgery **B:** CHT neoadj + surgery **C:** RT 1.75Gy/fr to 35 Gy + surgery **D:** CHT, same as B + RT, same as C + surgery	1983–1988 SCC, T1–2 NX M0 186/217 pts eligible A 41 pts B 50 pts C 48 pts D 47 pts

ADC: adenocarcinoma; C: randomized controlled trial; CHT: chemotherapy; co: concomitant; CHRT: chemoradiotherapy radiotherapy; CRT: chemoradiotherapy; fr: fraction; MST: median survival time; neoadj: neoadjuvant; ns: not significant; OS: overall survival; PFS: progression free survival; SCC: squamous cell carcinoma; RT: radiotherapy; w: week; y: years CHT ref [28]: cisplatin 20 mg/m^2 + bleomycin 5 mg/ m^2 x 2/d, d 1–5 and d 15–19 before RT.

Results			Conclusion/Comments
	OS% at 2 y	**5 y**	No evidence that preop RT improves the survival of patients with potentially resectable oesophageal cancer. **M1**
A	30	15	
B	34	18 ns	
	OS% at 5 y		Low dose preop RT offered no advantage. **C2**
A	13		
B	13		
	OS% at 5y		Radiation doses poorly reported. A whole body dose is reported! No benefit of preop RT. High doses per fraction. Postoperative mortality 23%! **C3**
A	11.5		
B	9.5 ns		
	OS% at 5 y		Fractionation schedule not reported! For pts with good tumour response after RT overall survival 50% at 5 y. **C3**
A	30		
B	35 ns		
	OS% at 5 y	**MST, w**	No benefit of preoperative RT. **C1**
A	9	48	
B	10 ns	49 ns	
	OS% at 3 y		Preop RT significantly improves survival, while preop CHT does not. At least two deaths probably related to CHT. Female patients had a significantly better survival than males. **C1**
A	9		
B	3		
C	21		
D	17		
A vs B	ns		
A/B vs C/D	p=0.009		

Overview 1b *Resectable oesophageal cancer.*
Preoperative chemo-radiotherapy + surgery versus surgery alone.

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Bosset 1997 [10] C	**A:** surgery **B:** CHT neoadj + RT 3.7 Gy/fr, 5 fr, split 2 w, then another 5 fr, total dose 37 Gy + surgery	1989–1995 SCC, T1–3 N0–1 M0 282/297 pts eligible A 139 pts B 143 pts
Le Prise 1994 [27] C	**A:** surgery **B:** CHT neoadj +RT 2.0 Gy/fr to 20 Gy + surgery (on d 42)	1988–1991 SCC, stage I and II 86/104 pts eligible A 45 pts B 41 pts
Urba 2001 [38] C	**A:** surgery alone **B:** RT 1.5 Gy _ 2/d to 45 Gy + CHT co + surgery on day 42	1989–1994 SCC (25%) or ADC (75%) 100 out of 217 eligible pts were randomized A 50 pts B 50 pts
Walsh 1996 (39) C	**A:** surgery alone **B:** RT, 2.67 Gy/fr to 40 Gy, + CHT co + surgery week 8	1990–1995 113 pts with ADC A 54/55 eligible pts B 48/58 eligible pts
Nygaard 2nd Scand trial 1992 [28] C Included in meta-analysis [7], (only groups A and C)	**A:** surgery **B:** CHT neoadj + surgery **C:** RT 1.75Gy/fr to 35 Gy + surgery **D:** CHT, same as B + RT, same as C + surgery	1983–1988 SCC, T1–2 NX M0 186/217 pts eligible A 41 pts B 50 pts C 48 pts D 47 pts

CHT ref [10]: cisplatin 80mg/m^2 0–2 d before each RT course.
CHT ref [27]: cisplatin 100mg/m^2 d 1 + 21 and 5-fluorouracil 600mg/ m^2 d 2–5 + d 22–25, before RT
CHT ref [38]: cisplatin 20 mg/m^2/d, days 1–5 and 17–21 + 5-fluorouracil 300 mg/m^2/d, days 1–21 + vinblastin 1mg/m^2/d, days 1–4 and 17–20
CHT ref [39]: 5-fluorouracil 15 mg/kg/day, days 1–5 + cisplatin 75 mg/m^2, day 7, repeated week 6
CHT ref [28]: cisplatin 20 mg/m^2 + bleomycin 5 mg/ m^2 x 2/d, d 1–5 and d 15–19 before RT.

Results	Conclusion/Comments
MST 18.6m in both groups **DFS** prolonged in A compared to B (numbers NR) p<0.003.	Unconventional fractionation schedule. No survival benefit of CHRT. Increased number of postop deaths in the combined-treatment group probably due to deleterious effects of the high dose of radiation per fraction or of CHRT on lung tissue. **C2**
OS% at 3 y A 13.8 B 19.2 ns MST 10m in both groups	The preoperative radiation dose was low. No impact on survival. **C2**
OS% at 1 y **3 y** **DFS%** A 58 16 16 B 72 30 ns 28 ns MST A: 17.6 m vs B: 16.9 m	117 pts were excluded, 73 refused, 10 due to medical contraindications, 18 due to pathology, 6 due to previous treatment, 4 due to multiple cancers and 6 for miscellaneous reasons. Median follow-up 8.2 years. 28% of patients in B had no residual cancer in the resected oesophagus. Large proportion of adenocarcinomas (75%). No statistically significant survival difference between the two treatment arms. **C2**
OS% at 1y **2y** **3y** A 44 26 6 B 52 37 32 p<0.01 MST A: 11 m; B: 16 m, p <0.01	17% of the pts in arm B were withdrawn because of protocol violations. Significant survival advantage with preop CHRT. 25% of the 58 patients assigned to preop CHRT had a complete pathological response after resection. **C2**
OS% at 3 y A 9 B 3 C 21 D 17 A vs B ns A/B vs C/D p=0.009	Preop RT significantly improves survival, while preop CHT does not. At least two deaths probably related to CHT. Female patients had a significantly better survival than males. **C1**

Overview 2 *Resectable oesophageal cancer.*
Surgery alone versus surgery + postoperative radiotherapy.

Author Year (ref no) Design	Aim/ Study question	Patient population
Fok 1993 [13] C	**A:** Curative surgery **B:** Curative surgery + RT 3.5 Gy/fr, 3 fr/w to 49 Gy **C:** Palliative surgery **D:** Palliative surgery + postop RT 3.5 Gy/fr, 3 fr/w to 52.5 Gy B 30 pts C 35 pts D 35 pts	1986–1989 SCC or ADC 130/221 pts eligible A 30 pts
Teniere 1991 [37] C	**A:** Surgery **B:** Surgery + postop RT 1.8 Gy/fr to 45 Gy (N0 pts) or 55 Gy (N+ pts)	1979–1985 221 pts with SCC in lower two-thirds of oesophagus A 119 pts B 102 pts
Zieren 1995 [44] C	**A:** Surgery **B:** Surgery + postop RT 1.8 Gy/fr to 30.6 Gy + boost to 55.8 Gy	1988–1991 68 pts with SCC, T1–4 N0–1 M0–1 (lym), Stage II–IV A 35 pts B 33 pts

ADC: adenocarcinoma; C: randomized kontrolled trial; CHT: chemotherapy; co: concomitant; CHRT: chemoradiotherapy; fr: fraction; ITT: intention to treat; m: month(s); lym: lymphnode metastases; MST: median survival time; neoadj: neoadjuvant; ns: not significant; OS: overall survival; PFS: progression free survival; QoL: quality of life; SCC: squamous cell carcinoma; RT: radiotherapy; w: week(s); y: year(s)

Results				Conclusion/Comments
	OS%	**MST, m**		91 pts excluded, 38 due to postop complications, 35 due to poor performance, 18 due to metastatic diseases. Shorter survival after postop RT due to ulcers and bleeding in the oesophageal substitute in groups B+D. High fractionation doses. Less frequent local recurrence after palliative surgery + postop RT (D) compared to surgery alone (C), 20% vs 46%, p<0.04 **C3**
A+C	37	15.2		
B+D	6	8.7		
	p <0.0001	p <0.02		
	OS% at 5 y	**MST, m**		No benefit of postop RT, which was allowed to start as late as 3 months after surgery. 5 y OS was sign better for N0-patients compared to N+ (38% vs 7%, p<0.01) **C2**
A	19	18		
B	19	18		
	OS%			No benefit with postop RT. Increased frequency of fibrotic strictures; worse QoL after postop RT. **C2**
	1 y	**2 y**	**3 y**	
A	53	31	20	
B	57 ns	29 ns	22 ns	

Overview 3 *Resectable oesophageal cancer. Comparison between surgery and radiotherapy and between different pre- and postoperative treatments.*

Author Year (ref no) Design	**Aim/ Study question**	**Patient population**
Badwe 1999 [9] C	**A:** Surgery **B:** RT 1.8 Gy/fr to 50 Gy + boost: 1.8 Gy/fr to 15 Gy or intraluminal brachytherapy, 15 Gy at 1 cm off axis	1993–1994 99/120 pts eligible with SCC A 43/47 analysed pts B 44/52 analysed pts
Andersen 1st Scand trial 1984 [5] C	For resectable tumours **A:** RT 1.75 Gy/fr to 35 Gy + surgery **B:** RT 1.5 Gy/fr to 30 Gy + CHT co + surgery For inoperable tumours **C:** RT 1.75 Gy/fr to 63 Gy **D:** RT 1.5 Gy/fr to 55 Gy + CHT co	1977–1981 278 pts with SCC, 57 pts excluded due to distant metastases A 59/63 pts eligible B 65/70 pts eligible C 42/44 pts eligible D 40/44 pts eligible
Kelsen 1990 [21] C	**A:** 1. RT 2 Gy/fr to 40 Gy + boost 2.5 Gy/fr to 15 Gy, total dose 55 Gy + surgery. 2. RT, 1.8 Gy/fr to 45 Gy + boost 1.8 Gy to 10 Gy, total 55 Gy + surgery **B:** CHT neoadj + surgery.	1981–1987 96 pts with SCC + NSCC A 48 pts, 35 treated with A1, 13 according to A2 B 48 pts
Iizuka 1988 [20] C	**A:** RT 2Gy/fr to 30Gy + surgery + postop RT 2 Gy/fr to 24Gy to total dose 54Gy, (50Gy to supraclavicular area and upper mediastinum) **B:** surgery + postop RT, 2Gy/fr to 50Gy	1982–1983 SCC, Stage I–III 207/364 pts eligible A 104 B 103
JEOG 1993 [1] C	**A:** Surgery + postop RT, 2 Gy/fr to 50 Gy **B:** Surgery + postop CHT	1985–1987 T1–4 N0–1 M0 253/258 pts eligible A 127 pts B 126 pts

Results	Conclusion/Comments
OS% at 3 y A 40 B 8 p=0.002 OS figures estimated from survival curves.	3 pts in A were excluded, 2 due to metastases and 1 received RT and was analysed in B. 10 pts in B were excluded, 7 due to RT given at other treatment centres, 3 due to no RT. Analysis with ITT did not change the results. Surgery was twice as likely to result in improvement in swallowing at 6 m, but no difference at 9 m as compared with RT. **C2**
MST, w **OS% at 2 y** A 26 18.6 B 25 24.6 C 27 11.9 D 23 12.0 ns	No benefit of bleomycin + RT vs RT alone in either resectable or medically inoperable tumours (due to poor general condition). **C1**
MST, m A 12.4 B 10.4 ns 55% in A and 58% in B resectable. Op mortality 13.5% (A) vs 11% (B).	No significant difference in response rate between the two groups. Since the majority of pts received postop crossover-treatment, comparison of survival in the two groups is not possible. **C3**
MST, d A 394 B 648 p <0.007	Postop RT gave better survival rate than preop RT + postop RT. 43% noneligible pts due to inoperability (21%) or postop complications (22%). More females (who usually do better) in arm B. **C2**
OS% **1y 2y 3y 4y 5y** A 80 61 51 46 44 B 90 60 52 47 42 ns	Histology NR. Overall good survival rates, but no statistical difference between the two groups. Low CHT-doses by Western standards, but at a level consistent with the general policy in Japan. **C2**

The table continues on the next page

Overview 3 *continued*

Author Year (ref no) Design	Aim/ Study question	Patient population
Hosokawa 1999 [18] C	**A:** Surgery + IORT 25 Gy + postop RT 2.8 Gy/fr to 45 Gy **B:** Surgery + IORT 20 Gy + postop RT same as A **C:** Surgery + IORT 18 Gy + postop RT same as A **D:** Surgery + IORT 15 Gy + postop RT same as A **E:** surgery + IORT 12 Gy + postop RT same as A	1989–1991 SCC 40 pts randomized to A or B A 18 pts B 22 pts 1991–1995 68 pts randomized to C or D C 38 pts D 30 pts 1995– not randomized pts E 13 pts
Kitamura 1995 [22] C	Hyperthermia **A:** RT 2 Gy/fr to 30 Gy + CHT co + surgery after 7–10 d **B:** Same RT and CHT as A + hyperthermia to 42.5–44.0 °C for 30 min x 2/w + surgery as in A	1988–1992 66 pts with SCC A 34 pts B 32 pts

C: randomized controlled trial; CHT: chemotherapy; co: concomitant; fr: fraction; IORT: intraoperative radiotherapy; MST: median survival time; neoadj: neoadjuvant; ns: not significant; OS: overall survival; SCC: squamous cell carcinoma; RT: radiotherapy; w: week; y: years;
CHT ref [5]: bleomycin, 5mg i.m. before each fraction, to a total dose of 100 mg.
CHT ref [21]: cisplatin 120 mg/m^2 or 3 mg/kg (whichever was less), d 1 and 29 + vindesin 3 mg/m^2 d 1, 8, 15, 22, 29, 36 and 43 + bleomycin 10000 IE/m2 i.v.as bolus followed by continuous infusion 10000 IE/m^2/d
CHT ref [1]: cisplatin 50 mg/m^2 + vindesin 3 mg/m^2 on day 1, repeated twice at an interval of 3 weeks
CHT ref [22], 1980–1990: bleomycin 5 mg i.v., twice a week, total dose 30 mg,
1991–1992: cisplatin 50 mg iv, once a week to total dose 150 mg

Results		Conclusion/Comments
	OS% at 5 y	No significant difference in the overall survival rate between groups. 4 fatal tracheal ulcers (22.2%) occurred in group A. No ulcers with lower doses. **C3**
A	17.6	
B	38.9	
C	34.5	
D	34.1 ns	
E	follow-up to short	
	OS% at 3 y	HCHRT demonstrates better results not only in local control but also in long-term effects, compared with CHRT. Similar survival curves for both groups during the first year, thereafter separation. **C2**
A	24.2	
B	50.4	
	p <0.05	

Overview 4 *Inoperable oesophageal cancer,*
(Not reported whether surgically non-resectable or medically inoperable patients)
Radiotherapy versus chemo-radiotherapy.

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
al-Sarraf 1997 [4] C	**A:** RT 2 Gy/fr to 64 Gy **B:** RT 2 Gy/fr to 50 Gy + CHT co + adj	1986–1990 SCC or ADC, T1–3 N0–1 M0 123/129 pts eliglible A 62 pts B 61 pts
Araujo 1991 [6] C included in meta-analysis [43]	**A:** RT 2 Gy/fr to 50 Gy **B:** RT same as A + CHT co	1982–1985 59 pts with SCC, stage II A 31 pts
Cooper RTOG 85–01 1999 [11] C included in meta-analysis [43]	Same as ref [4]. 69 non-randomized pts treated according to group B.	1986–1990 123/129 pts from ref 4 + 69 non-randomized pts 1990–1991 A 62 pts B 61 + 69 pts
Hatlevoll 2nd Scand trial 1992 (15) C included in meta-analysis [43]	**A:** RT 1.75Gy/fr to 63 Gy, split course **B:** CHT neoadj + RT same as A	1983–1988 97 pts A 51 pts B 46 pts
Herskovic 1992 [16] C	**A:** RT 2 Gy/fr to 64 Gy **B:** RT 2 Gy/fr to 50 Gy + CHT co + adj	1986–1990 121/129 pts eligible with SCC or ADC A 60 pts B 61 pts

Results	Conclusion/Comments
OS% at 5 y A 0 B 27 p <0.0001 MST (m) 9.3 group A vs 14.1 group B, p=0.0001	Different radiotherapy doses in the two groups. CHRT superior to RT. Well planned and done study. Only progress report, final results reported in Cooper 1999 (ref 11) **C2**
OS% at 5 y A 6 B 16 ns B 28 pts	Only one course of chemotherapy. One patient with radiation myelitis in the RT-group after 24 months. No benefit of CHRT over RT alone. **C2**
OS% at 5 y A 0 B 26 p <0.001	This study is a continuation of ref. 4 where a cohort of 69 pts were treated according to group B, without randomization. The final analysis comprises pts in ref. 4 and ref. 11. Different radiotherapy doses in the two groups. Early termination after interim analysis, 1990. CHRT superior to RT. **C1**
OS% at 3 y A 6 B 0 ns	Prolonged treatment; RT during 10 weeks, CHRT during 13 weeks. No benefit of CHRT over RT alone. **C2**
OS% 1 y 2 y A 33 10 B 50 38 p<0.001 MST (m) 8.9 group A vs 12.5 group B, p<0.001	Trial closed after 121 pts (150 planned), due to significant advantage for the CHRT-group, as measured by local control (p<0.02), distant metastases (p<0.01) and survival, but at the cost of increased side effects. Unequal racial balance in the treatment groups in favour of the CHRT groups. **C1**

The table continues on the next page

Overview 4 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Alberts 1984 [2] C	All groups RT 5 Gy/fr to 25 Gy. 4 w split, then a 2nd RT course: **A_1:** RT 5 Gy/fr to 25 Gy, total dose 50 Gy **A_2:** RT 3 Gy/fr to 30 Gy, total dose 55 Gy **$B_{1,2}$:** RT as in A1 or A2 + CHT1 co **$C_{1,2}$:** RT as in A1 or A2 + CHT2 co **$D_{1,2}$:** RT as in A1 or A2 + CHT3 co	272 pts A 65 pts B 76 pts C 67 pts D 64 pts
Earle ECOG 1980 [12] C included in meta-analysis (43)	**A:** RT 2.0 Gy/fr to 50–60 Gy **B:** RT as in A + CHT co	1974–1978 77/91 pts eligible with SCC A 37/44 pts eligible B 40/47 pts eligible
Hukku 1989 [19] C	**A:** RT 2.3 Gy/fr to 35 Gy + boost after a split of 2 w **B:** RT as in A + CHT co	1984–1985 70/74 pts eligible with SCC A 44 pts B 26 pts
Roussel 1989 [30] C included in meta-analysis [43]	**A:** RT 2.25 Gy/fr to 56.25 Gy **B:** RT same as A + CHT co	1976–1982 SCC 150/170 pts eligible A 73 pts B 77 pts
Wobbes 2001 [42] C	**A:** RT 4 Gy/fr to 20 Gy, 2 w split, 4 Gy/fr to 20 Gy, total dose 40 Gy/4 w **B:** RT same as A + CHT neoadj + adj	1983–1989 SCC, st T1–3, N0–1, M0 203/211 pts eligible A 101 pts B 102 pts
Smith ECOG, EST-1282 1998 [35] C	**A:** RT 1.8 Gy/fr to 40 Gy, then either surgery or RT to total dose 60 Gy **B:** RT ± surgery same as A + CHT co	1982–1988 SCC, stage I and II 119/135 pts eligible A 60 pts B 59 pts

Results	Conclusion/Comments
OS% at 1 y A 13.0 B 7.6 C 2.3 D 7.7 ns MST (w): 12, 11, 11, 15 for group A, B, C, D	Published in African. Time-span not described. Short median survival. High fractionation doses in RT. Double randomization. No benefit for CHRT over RT alone. **C3**
MST A 6.4 m B 6.2 m, n.s.	One third of the pts received 50 Gy and the rest 60 Gy. No benefit for CHRT over RT alone. **C2**
Response rate (CR+PR) **OR% DFS% OS%, at 2 y** A 68.2 4.5 13.5 B 100 31 54.0 p<0.05	No explanation to the imbalance between the groups. Adequate randomization? The boost dose is NR. Significant advantage for CHRT over RT alone. **C3**
OS% **1 y 3 y MST (m)** A 35 6 8 B 31 ns 12 ns 9 ns	No benefit of CHRT compared to RT is demonstrated. Severe hematological toxicity in 7.8% in group B. Important prognostic factors are performance status and weight loss. **C1**
OS% **1 y 2 y PFS, m** A 29 15 5 B 45 20 6.9 p <0.03 MST (m) 7.9 group A and 9.6 group B, p <0.05	Imbalance in T-stage between the two groups had a favourable impact on survival in group A. Survival curves became similar after 2 years. Haematological tox more common in CHRT arm (6% vs 1%). Appart from that the combination treatment was well tolerated and should be preferred to radiotherapy alone. **C1**
OS% **2 y 5 y** A 12 7 B 27 9 ns MST (m) 9.2 group A vs 14.6 group B	Since 37% of the patients underwent surgery which was elective and not randomized, the comparison of survival was subject to selection bias. **C3**

The table continues on the next page

Overview 4 *continued*

Author **Year (ref no)** **Design**	**Aim/** **Study question**	**Patient population**
Slabber 1998 [34] C included in meta-analysis [43]	**A:** RT 4 Gy/fr d 1–5 and 29–33 to 40 Gy **B:** RT same as A + CHT co	1991–1995 SCC, T3 N0–1 M0 70 pts A 36 pts B 34 pts
Wong 2001 [43] M (Cochrane analysis)	**A:** RT alone **B:** CHRT	769 pts concomitant CHT 453 pts sequential CHT
Andersen 1st Scand trial 1984 [5] C included in meta-analysis [43]	For resectable tumours **A:** RT 1.75 Gy/fr to 35 Gy + surgery **B:** RT 1.5 Gy/fr to 30 Gy + CHT co + surgery For medically inoperable tumours **C:** RT 1.75 Gy/fr to 63 Gy **D:** RT 1.5 Gy/fr to 55 Gy + CHT co	1977–1981 278 pts with SCC, 57 pts excluded due to distant metastases A 59/63 pts eligible B 65/70 pts eligible C 42/44 pts eligible D 40/44 pts eligible

ADC: adenocarcinoma; C: randomized controlled trial; CHT: chemotherapy; co: concomitant;
CHRT: chemoradiotherapy; fr: fraction; m: month(s); MST: median survival time; neoadj: neoadjuvant; ns: not significant;
OR: overall response; OS: overall survival; PFS: progression free survival; SCC: squamous cell carcinoma; RT: radiotherapy;
w: week(s); y: year(s)

CHT ref [4,11]: cisplatin 75mg/m^2 d 1 + 5-fluorouracil 1000 mg/m^2 d 1–4, 4 cycles during and after RT.
CHT ref [6]: 5-fluorouracil 1000mg/m^2 d 1–3 + mitomycin 10mg/m^2 d 1 + bleomycin, 15000 IU weekly x 5 during RT.
CHT ref [15]: cisplatin 20mg/m^2 + bleomycin 10000 IU/m^2 d 1–5 and d 15–19 before RT.
CHT ref [16]: cisplatin 75mg/m^2 d 1 + 5-fluorouracil, 1000mg/ m^2, d 1–4, 4 cycles during and after RT.
CHT ref [2]: CHT1: vinblastine 10 mg d 1 of each RT course.
CHT2: bleomycin 15 000 IE d 1 and 30 000 IE d 2 and 3 of each RT course.
CHT3: vinblastine 10 mg d 1 + bleomycin 15 000 IE d 1 and 30 000 IE d 2 and 3 of each RT course.
CHT ref [12]: bleomycin 15 mg each day of RT until a total dose of 210 mg.
CHT ref [19]: bleomycin 15 mg + 5-fluorouracil 500 mg i.v. biweekly during RT.
CHT ref [30]: methotrexate 6 mg/m^2 /d, d 1–4 during RT.
CHT ref [42]: cisplatin 100 mg/m^2 d 3–4, before RT and 5 cycles after RT every 3–4 w.
CHT ref [35]: 5-fluorouracil 1000 mg/m^2 d 2–6 and 28–32 + mitomycin 10 mg/m^2 d 2.
CHT ref [34]: cisplatin 15 mg/m^2/d + 5-fluorouracil 600 mg/m^2/d d 1–5 and 29–33
CHT ref [5]: bleomycin, 5mg i.m. before each fraction, to a total dose of 100 mg.

Results			Conclusion/Comments
	MST, d		No statistical significant difference between CHRT and RT alone.
A	144		**C2**
B	170, n.s.		
Significant reduction in local recurrence for pts treated with concomitant CHRT compared with RT alone (p=0.004). No significant difference with sequential CHRT compared with RT alone (p=0.26). 9% survival benefit at 1 and 2 y with concomitant CHRT.			Concomitant CHRT significant better than RT alone in reducing local recurrence. Slightly better survival with concomitant CHRT, but not with sequential CHRT compared with RT alone. **M1**
	MST, w	**OS% at 2 y**	No benefit of bleomycin + RT vs RT alone in either resectable or medically inoperable tumours (due to poor general condition). **C1**
A	26	18.6	
B	25	24.6	
C	27	11.9	
D	23	12.0 ns	

Overview 5 *Inoperable oesophageal cancer.*
(Not reported whether surgically non-resectable or medically inoperable patients).
Different radiation doses and fractionation schedules.

Author Year (ref no) Design	Aim/ Study question	Patient population
Shi 1999 [33] C	**A:** RT 1.8 Gy/fr to 68.4 Gy **B:** RT 1.8 Gy/fr to 41.4 Gy + boost 1.5 Gy/fr, 2 fr/d, to 27 Gy, to total dose 68.4 Gy	1988–1990 85 pts with SCC A: 42 pts B: 43 pts
Wan 1991 [40] C	**A:** RT 2.0 Gy/fr 1 fr/d to 70 Gy **B:** RT 1.67Gy/fr 3 fr/d to 50Gy	1981–1983 172 pts with midsegment carcinomas less than 8 cm in diameter A 90 pts B 82 pts
Holsti 1969 [17] C	**A:** RT 1.7 Gy/fr to 57–63Gy in 1 series **B:** RT 1.7 Gy/fr to 57–63 Gy in 2 series with 2–3 w split	1964–1965 45 pts were randomized and 87 non-randomized pts were added A 74 pts B 58 pts
Okawa JASTRO 1999 [29] C	**A:** RT 2.0 Gy/fr to 60 Gy + boost 2.0 Gy/fr to10 Gy with external RT **B:** RT 2.0 Gy/fr to 60 Gy + boost 5.0 Gy/fr to 10 Gy with intraluminal brachytherapy	1991–1995 94/103 pts eligible A 51 pts B 43 pts
Sur 1998 [36] C	**A:** BRT 12 Gy/2 fr, weekly, 1 cm from source axis **B:** BRT 16 Gy/2 fr, same as A **C:** BRT 18 Gy/3 fr, same as A	1994–1995 172 pts with inoperable SCC or ADC A 35/36 pts eligible B 60/68 pts eligible C 55/68 pts eligible

BRT: brachy therapy; CSS: cause specific survival; fr: fraction; HDR: high dose rate; LCR: local control rate;
MST: median survival time; ns: not significant; OS: overall survival; y: year(s)

Results	Conclusion/Comments
OS% DFS% LCR%, at 5y A 15 15 21 B 34 42 55 p=0.022 p=0.011 p=0.003 MST, m A: 11.2 , B: 29.3, p=0.03	Accelerated hyperfractionated RT is superior to conventional RT to the price of more acute radiation-induced bronchitis and oesophagitis. **C1**
OS% at 5 y 12% in both groups	Low total dose in the hyperfractionated group. Much more acute and late effects in A compared to B. **C3**
OS% at 1 y 2 y A 23 16 B 42 21	Survival data presented for a mix of randomized and non-randomized pts. No statistical evaluation done. **C3**
CSS% at 2 y 5 y for pts with <5 cm tumour length A 39.4 31.5 B 74.6 64.0 p= 0.025	Better survival rate in a subgroup of patients with small tumours with combination of external and intraluminal radiotherapy compared with external radiotherapy alone. **C2**
OS% at 1 y A 9.8 B 22.5 C 35.3 ns MST 6.2 m for all groups	A preliminary analysis of 68 pts who had completed 6 m follow-up showed that pts in group A did significantly worse than pts in groups B and C. Group A therefore discontinued and pts were randomized only to groups B and C. Multivariate analysis showed that higher brachytherapy dose had a significant effect on OS (p=0.002) but also increased frequency of fibrotic strictures. Best palliative dose lies in the range of 16 Gy in two fractions and 18 Gy in 3 fractions weekly. **C2**

Overview 6 *Inoperable oesophageal cancer (Not reported whether surgically non-resectable or medically inoperable patients). Miscellaneous treatments.*

Author Year (ref no) Design	**Aim/ Study question**	**Patient population**
Schmid 1993 [32] C	**A:** Intubation only **B:** Intubation + RT 4 Gy/fr to 40 Gy, with 5 w split **C:** Intubation + CHT C: 35/40 pts eligible	1987–1989 127 pts with SCC A: 45/46 pts eligible B: 37/41 pts eligible
Alberts 1992 [3] C	**A:** Intubation only **B:** Intubation + RT 4Gy/fr to 40Gy, with split + CHT co	20 pts with SCC A 10 pts B 10 pts
Sargeant 1997 [31] C	**A:** laser recanalisation **B:** laser recanalisation + RT 3 Gy/fr to 30Gy	1990–1992 67 pts with inoperable SSC or ADC A 30 pts B 37 pts
Kolaric 1977 [23] C	**A:** CHT1 **B:** CHT2 + RT 2 Gy/fr to 38–44 Gy B 15 pts	33 inoperable pts A 18 pts B 60 $p<0.05$
Kolaric 1980 [25] C	**A:** CHT1 **B:** CHT2 + RT 2Gy/fr to 36–40 Gy	31/33 inoperable pts with all histologic sub-types A 16 pts B 15 pts
Kolaric 1980 [24] C	**A1:** CHT1 **A2:** CHT2 = ref 23 **A3:** CHT3 = ref 24 **B1:** CHT1 + RT 2 Gy/fr to 38–44 Gy **B2:** CHT2 + RT 2 Gy/fr to 38–44 Gy **B3:** CHT3 + RT 2 Gy/fr to 36–40 Gy	103/115 inoperable pts A 49 pts (includes pts in ref 23 and 24) B 54 pts

ADC: adenocarcinoma; C: randomized controlled trial; CHT: chemotherapy; co: concomitant;
CHRT: chemoradiotherapy;r: fraction; HCHRT: hyperthermic chemoradiotherapy; m: month(s);
MST: median survival time; NR: not reported; ns: not significant; OR: overall response; OS: overall survival;
RT: radiotherapy; SCC: squamous cell carcinoma; w: week(s); y: year(s);
CHT ref [32]: trimetrexate 12 mg/m^2 i.v. daily for 5 d every 28 d (10 pts) or ifosfamide 1.2 g/m^2 for 5 d + Mesna 20% (10 pts) or 5-fluorouracil 425 mg/m^2 i.v. + leucovorin 20 mg/m^2 i.v. daily for 5 d every 28 d (20 pts)
CHT ref [3]: cisplatin 15 mg/m^2 d 1–5 + 5-fluorouracil 600 mg/m^2 d 1–5, 2 cycles during RT
CHT1 ref [23]: doxorubicin 40 mg/m^{2}2 d 1 and 2 for 6 cycles with an interval of 3 w.
CHT2 ref [23]: doxorubicin 40 mg/m^2 d 1 and 2 for 3 cycles with an interval of 3 w, co with RT.
CHT1 ref [25]: bleomycin 15 mg/m^2 d 1 and 4 + doxorubicin 40 mg/m^2 d 2 and 3 for 5–6 cycles at an interval of 3 w.
CHT2 ref [25]: bleomycin 15 mg/m^2 d 1 and 4 + doxorubicin 30 mg/m^2 d 2 and 3 for 2 cycles co and a third cycle 1 m after RT.
CHT1 ref [24]: bleomycin 15 mg/m^2 twice a week to a total dose 200–350 mg.
CHT2 ref [24]: as in ref [23].
CHT3 ref [24]: as in ref [25].

Results	Conclusion/Comments
MST, w A 15 B 9 C 11 ns	Intubation is considered to be the most practical form of palliation in South Africa. Additional palliative radiotherapy or single-agent cytostatic treatment in patients with good performance status does not alter the natural history of the disease. **C3**
MST, w A 19 B 11 ns	Published as letter. Inclusion time NR. 4 treatment related deaths in CHRT-groups made early termination of this trial ethically necessary, therefore few patients. **C3**
MST 5 m in both arms (estimated from survival curve)	The time to retreatment increased from 5 to 9 weeks with RT, p<0.01. No significant difference in survival with or without RT. **C3**
OR% A 33	Inclusion time NR. The irradiation given with a single 42 MeV electron field. Significantly better response rate with CHRT compared with CHT alone. **C3**
OR% **OS% at 1 y** A 19 1 pt B 60 p <0.01 7 pts	Inclusion time NR. The irradiation given with a single 42 MeV electron field. Significantly better response rate with CHRT compared with CHT alone. **C3**
OR% **OS% at 1 y** **2 y** A 27 6 0 B 61 39 24 p not reported	In this report ref 23 and ref 24 are included. Inclusion time NR. The irradiation given with a single 42 MeV electron field. Significantly better response rate with CHRT compared with CHT alone and prolonged survival. **C3**