

# Pharyngo-Cutaneous Fistulae After Laryngectomy

## Influence of Previous Radiotherapy and Prophylactic Metronidazole

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The development of a pharyngocutaneous fistulae is a major complication after total laryngectomy. In Denmark radiotherapy is the primary treatment for all laryngeal carcinomas. Based on the experience with conventional daily irradiation, a split-course radiation schedule was introduced in 1978. The charts of 106 consecutive patients laryngectomized for recurrence in the years 1975 to 1984 were examined. Thirty-four patients developed a fistula. An evaluation of the different radiotherapy schedules used during this period allowed a dose-response curve to be constructed. It showed a pronounced increase of fistulae with high doses of radiotherapy. Split-course radiotherapy caused a rise in late complications and did not improve tumor control. Large field sizes increased the number of fistulae. High-dose fractions showed a surprisingly high incidence of late complications. Prophylactic metronidazole (introduced in 1980) resulted in a highly significant decrease in the frequency of postoperative fistulae. Patients in whom fistula formed were hospitalized for an average of 54 days, patients without, for 22 days.

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THE INCIDENCE OF SQUAMOUS CELL carcinoma of the larynx shows a rising trend, especially in men. This trend is reflected in the increase from 154 to 235 in the annual Danish cases from 1971 to 1980.<sup>1</sup> Radiotherapy, with the objective of preserving the laryngeal function, is the primary treatment for all laryngeal carcinomas in Denmark. Patients have been treated with relatively low doses of radiation in order to avoid complications, and laryngectomy has only been performed in case of recurrence. However, such "salvage surgery" is becoming a more frequent procedure because of the rising incidence of the disease.

Pharyngocutaneous fistula, a serious complication following laryngectomy, must be avoided not only for the patient's sake, but also for economic reasons. The large variation in the incidence of fistulae (7.4% to 65%) reported in different studies<sup>2-24</sup> is a result of differences in initial treatment (surgery or radiotherapy) and the application of variable criteria in the selection of patients for surgery of recurrences.

The published reports dealing with fistulae suggest

many etiologic factors and propose implementing various measures to counter this complication as well as different techniques for repair once the damage has been done. The many different factors that have been reported to be significant in the etiology of fistulae include irradiation (*per se*), doses of radiation, radiation field size, postoperative hemoglobin level, preoperative tracheostomy, extent/methods of surgery, early removal of nasogastric tube, radical neck dissection, persistent carcinoma, extension of tumor to pharyngeal wall, and other diseases that occur simultaneously with laryngectomy.<sup>2-24</sup> The marked differences in the reported results hampers an assessment of their relative importance, notably with regard to the role of radiotherapy on which there is no agreement whatsoever. Some authors<sup>3,6,9,11,16,22,25,26</sup> find radiotherapy to be an important etiologic factor, while others find the same frequency of fistulae in irradiated and nonirradiated patients.<sup>2,5,8,10,17,24</sup>

In 1979 and 1980 analyses of results were presented on the treatment of laryngeal carcinoma using the Ellis and Cohen models on an Aarhus material for a 10-year period.<sup>25,26</sup> In short, it was concluded that better results could be obtained using a split-course schedule (Table 1, 72 Gy), which was expected to cause fewer locoregional recurrences without any (or with only a slight) increase in late complications.<sup>25,26</sup> Still, the treatment concept remained the same; that is, all patients should have the same initial treatment (no surgery, preservation of the

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TABLE 1. Tumor/Lymph Node/Distant Metastasis Classification According to International Union Against Cancer, 1978

	N0	N1	N2	All
T1a	26			26
T1b	11	1		12
T2	33	1	1	35
T3	21	3		24
T4	5	4		9
All	96	9	1	106

laryngeal function, thus keeping salvage surgery for recurrences). Split-course radiotherapy was consequently introduced in the management of laryngeal carcinoma in a nationwide study in October 1979.

The benefit of achieving locoregional control by primary treatment has previously been demonstrated.<sup>27,28</sup> The essence hereof is that improvement of the local treatment methods is expected to ensure a greater increase in the number of survivors than improvement of treatment for recurrence.

Studies published before 1980 have shown the effect of metronidazole in the treatment of anaerobic infections and in chemoprophylactic treatment of infection. Innes *et al.*<sup>29</sup> found that after introducing metronidazole as a prophylactic antibiotic (together with ampicillin and flucloxacillin), the rate of significant wound infection and pharyngocutaneous fistula formation was reduced from 35% to 10%. To our knowledge, no other investigations have dealt specifically with prophylactic antibiotics to laryngectomy patients.

This article will document the development of pharyngocutaneous fistulae in a 10-year study of consecutive patients who had salvage surgery for recurring la-

ryngeal carcinoma. The purpose of the study was to analyze the significance of radiotherapy (technique, time/dose/fractionation, field size), and metronidazole used in a prophylactic antibiotic regime.

### Patients and Methods

One hundred six consecutive patients with recurrent laryngeal squamous cell carcinoma underwent laryngectomy between January 1975 and December 1984. In this period no patients had laryngectomy as primary treatment for laryngeal carcinoma or sequelae after radiotherapy. The patients had been irradiated with the intent to cure the disease from 1965 to 1984, and the time from radiotherapy to laryngectomy varied from 6 weeks to 12.5 years. There were 14 women and 92 men. The mean age was 61 years (range, 43 to 78).

The classification of tumor was made according to the International Union Against Cancer (UICC) rules in 1978 (Table 1). (Patients admitted before 1978 have been reclassified). In Table 2 the sites of tumor origin are presented; 47% had a supraglottic tumor, and 52% had a glottic tumor.

### Radiation Treatment

All patients were treated with primary radiation by Cobalt 60 using two parallel opposed fields with a source to skin distance (SSD) of 80 cm. The patients were fixed in a cast and major tissue inhomogeneities were compensated for. A detailed description of the radiotherapy technique has been published.<sup>13</sup> Although the patients were treated over a wide time span, the radiotherapy technique was unaltered. All doses reported in this article refer to the central absorbed doses calculated at the mid-sagittal plane and the central axis. Patients given 57 Gy were treated with alternating fields. In all other patients both fields were irradiated at each fraction.

The fractionation schedule has been altered and adjusted several times, and the major shift from conventional, daily treatment to split-course therapy was introduced in Aarhus in January 1978. The different schedules are shown in Table 3. Because of an unexpected high incidence of early complications, the split-course dose was reduced from 72 Gy to 68 Gy after 1 year.<sup>25</sup>

### Surgical Treatment

Total laryngectomy was the treatment chosen for 99 of the recurrences, and only seven patients had partial laryngectomy. Ninety-seven of the patients were operated upon by the same surgeon (OE). The operation was carried out as a conventional laryngectomy with a U-shaped flap (Gluck Soerensen-incision). The surgical technique has changed very little over the years, but, for

TABLE 2. Site of Origin and Fistula Formation in Relation to Region and Site

Region and site	No. of patients	Frequency of fistulae
Supraglottis	50 = 47%	19/50 (38%)
Posterior surface of suprahoid epiglottis	8	2/8 (25%)
Aryepiglottic fold	5	2/5 (40%)
Arytenoid area	4	2/4 (50%)
Infrahyoid epiglottis	12	5/12 (42%)
Ventricular bands	21	8/21 (38%)
Ventricular cavities	0	
Glottis	55 = 52%	15/55 (27%)
Vocal cords	54	15/54 (28%)
Anterior commissure	1	0/1 (0%)
Posterior commissure	0	
Subglottis	1 = 1%	0/1 (0%)
All	106 = 100%	34/106 (32%)

Note: Region and site according to International Union Against Cancer rules, 1978.

TABLE 3. Treatment Schedules

Period	Total dose	Fractionation schedule	No. of patients
Feb 1965–Dec 1974	57 Gy	Daily radiation, 30 Fx	5
Jan 1975–Dec 1977	60 Gy	Daily radiation, 30 Fx	32
Jan 1978–Dec 1978	72 Gy	Split-course, 40 Gy/20 Fx—3 wk—32 Gy/16 Fx	18
Jan 1979–Dec 1984	68 Gy	Split-course, 40 Gy/20 Fx—3 wk—28 Gy/14 Fx	44
Nov 1979–Dec 1984	61 Gy	Split-course, 33 Gy/ 8 Fx—3 wk—28 Gy/14 Fx	7

Fx: fractions.

example, Vicryl (Polyglactin 910, Ethicon Inc., Somerville, NJ) has replaced chromic catgut as the material used to close the pharynx (closed in one continuous layer).

Combined total laryngectomy and radical neck dissection were performed in 13% of the cases. If a fistula developed, the treatment was conservative with nasogastric tube feeding. Surgical intervention was only necessary in three patients.

#### *Prophylactic Antibiotic Regimen*

Metronidazole as prophylactic antibiotic has been administered together with penicillin to nearly all patients since January 1980. Treatment was started 24 hours before the operation. The dose of metronidazole was 500 mg 3 times a day and the dose of penicillin was one million units 2 times a day. Both were given in 8- to 10-days. Before 1980, most of the patients received penicillin alone, or it was sometimes but rarely combined with other antibiotics.

#### *Statistical Analysis*

The logit analysis was used to plot the dose-response curve, and the chi-square test was used to calculate the other figures and tables. A Mantel-Haenszel test was used when comparing treatment groups.

### **Results**

Pharyngocutaneous fistulae were found in 34 (32%) of the patients. This number includes even the smallest fistulae of which only seven lasted for 1 to 2 weeks. Eleven fistulae persisted for more than 8 weeks. One patient had the fistula even when he died 281 weeks after laryngectomy and three unsuccessful attempts at surgical closure. The topographic distribution of fistulae related to tumor site is shown in Table 2. Only one of the patients with partial laryngectomy developed a fistula that lasted for 1 week.

#### *Radiotherapy*

*Total dose/fractionation:* A dose-response curve (Fig. 1) was constructed on the basis of the experience gained

from the different radiation schedules and the frequency of fistulae that were removed by salvage surgery. As shown, there is a pronounced increase in the frequency of fistulae with larger doses of radiation (57 Gy: 1 in 4; 60 Gy: eight in 30; 68 Gy: 3 in 4, and 72 Gy: 12 in 13). None of the data used to construct the curve were from patients who had metronidazole as a prophylactic antibiotic.

Figure 2 compares daily radiation and split-course treatment with a total dose of 60 Gy and 72 Gy, respectively (without metronidazole). The remarkably high incidence of fistulae in the split-course group was not associated with fewer locoregional recurrences. There was no difference in local control between the treatments, and, thus, the therapeutic ratio of locoregional control to number of fistulae.

*Influence of field size and time to laryngectomy:* A subgroup of patients was investigated to determine whether radiation field size and the "timing," defined as the time from radiation to laryngectomy, were instrumental in fistula formation. Figure 3 shows 29 patients who were treated with 60 Gy and who did not receive metronidazole at laryngectomy. No statistical association could be observed between the incidence of fistulae and time from radiation to surgery. We found instead that greater field size (greater than 50 cm<sup>2</sup>) induced an

TABLE 4. Frequency and Duration of Fistulae in Relation to Radiotherapy and  $\pm$  Metronidazole

Dose* Gy	No. of patients	Metronidazole $\pm$	Fistula	Median duration (wk)	Range (wk)
57	5	+1 -4	0/1 1/4	9.0	9
60	32	+2 -30	0/2 8/30	4.5	2-28
61	7	+7 -0	5/7 0/0	6.0	1-14
68	44	+39 -5	5/39 3/5	6.0 11.0	1-10 8-14
72	18	+5 -13	0/5 12/13	6.5	1-281

\*See treatment schedules in Table 3.

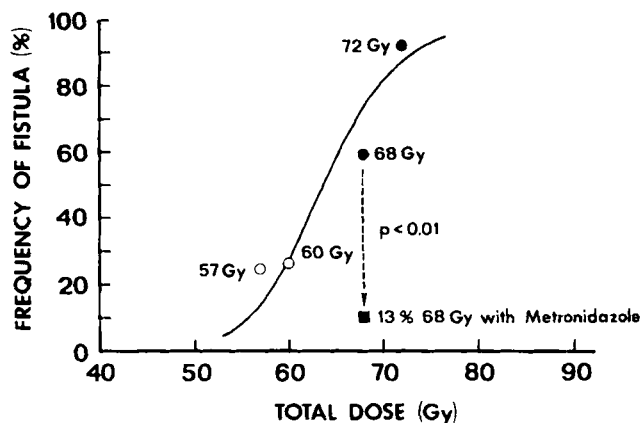


FIG. 1. Frequency of fistulae as a function of total dose (without metronidazole at laryngectomy). Open circles: daily radiation; closed circles: split-course radiation; square: split-course with metronidazole.

increase in the number of fistulae ( $P \cong 0.05$ ). Forty-two percent of the patients treated with large fields developed a fistula; small-field treatments induced fistulae in 13% of the patients.

**High dose per fraction:** A special problem arose with regard to a small group of patients (Fig. 4) who received split-course treatment with two high-dose fractions per week (4.13 Gy per fraction before pause; total dose, 61 Gy).<sup>30</sup> Seven patients treated in this way had a laryngectomy; all received metronidazole, but five (71%) developed a fistula. This schedule was not only apparently associated with serious, late complications, but also there was no improvement in local control.

**Prophylactic metronidazole:** As mentioned, combined prophylactic metronidazole and penicillin was introduced in January 1980. The different treatments are presented in Table 4, which shows frequency and duration of fistulae. Two groups of patients were treated with split-course radiotherapy at 68 Gy and 72 Gy, and only

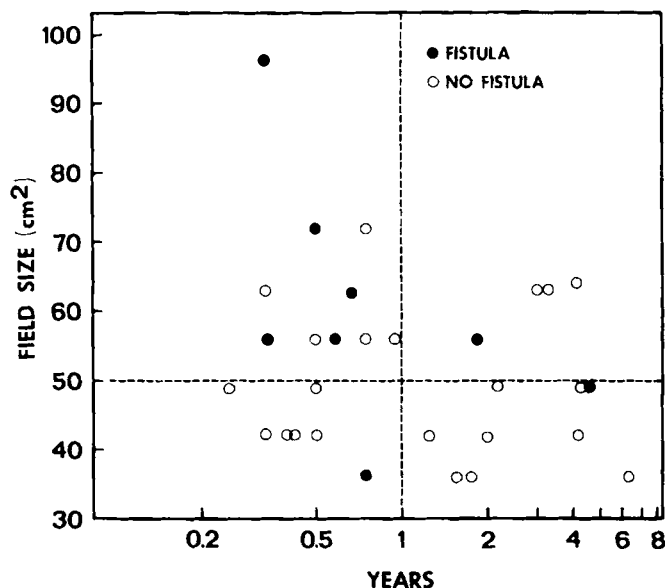


FIG. 3. Fistula formation as a function of time from radiation to laryngectomy and field size. All 30 patients received 60 Gy daily radiation and no prophylactic metronidazole at laryngectomy. Field size/fistulae: chi-square = 3.52;  $P \cong 0.05$ .

some in each group received metronidazole. When the results were analyzed, it appeared that metronidazole significantly reduced the number of fistulae in both groups (chi-square:  $P < 0.01$  and  $P < 0.001$ ). The reduction in the incidence of fistulae is highly significant when the Mantel-Haenszel test is used if the radiation dose is considered as a "confounder" ( $P < 0.001$ ). The drop in the frequency of fistulae for patients receiving 68 Gy (from 60% to 13%) is also shown in Figure 1.

#### Other Complications

Other major complications were carotid blowout (two patients) and recurring arterial bleeding from the base of

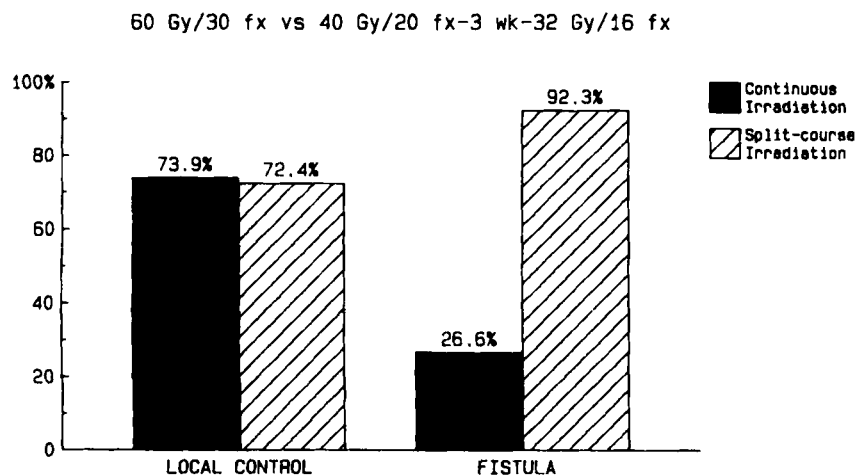
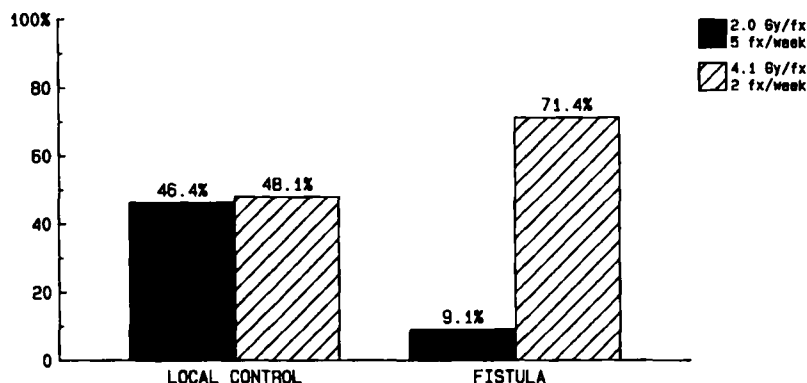


FIG. 2. Daily radiation compared with split-course radiation, all stages, without prophylactic metronidazole at laryngectomy.

FIG. 4. Normal dose compared with high dose per fraction in split-course radiation Stage II–IV. All patients had metronidazole at laryngectomy.



the tongue (one patient). One patient with carotid blow-out became a long-term survivor; the two others did not survive the postoperative period.

The development of fistulae was not found to be significantly influenced by postoperative hemoglobin level, preoperative tracheostomy, or radical neck dissection. Finally, fistula formation was not found to have any influence on the patient's prognosis.

Sufficient information on smoking habits has been collected since 1979. It appears that after this year, all 63 patients were smokers, many heavy smokers. (There was no data available for three patients).

### Discussion

The prolonged hospitalization resulting from fistula formation and the cost-raising effect require that the utmost be done to minimize complications from surgery. Patients with a fistula were hospitalized an average of 54 days, and patients without, 22 days, although this number has tended to drop over the past few years.

Our analysis reveals that there is a pronounced dose-response curve that is a direct function of the total radiation dose. In previous reports that focused on fistula formation where radiotherapy was considered a contributing factor, a dose-dependent complication rate was not demonstrated.<sup>3,6,9,11,16,22,25,26</sup>

Split-course radiotherapy for laryngeal carcinoma has been abandoned again in Denmark. The promising prospects offered in theory fell short of expectations, as we have shown in our analysis. The local control was not improved, and the number of late complications increased. Laryngectomy is still the treatment for recurrences, and primary continuous radiotherapy has been reintroduced. However, the current total dose of radiotherapy depends on the tumor size. The ensuing risk of more late complications must be accepted as an inherent feature of radiotherapy for patients with large tumors.

Lavelle and Maw<sup>17</sup> suggested that more fistulae will develop in relation to late laryngectomy, but as men-

tioned, we do not agree with this observation. However, we found a correlation between fistula formation and field size, but it must be realized that an advanced disease treated with large fields is often accompanied by early recurrence and a high incidence of fistulae. Other similar observations have been published.<sup>26</sup> This phenomenon has been allowed for in the design of an ongoing trial, where the large fields are reduced after 50 Gy so that only the tumor site is covered.

The patients treated twice a week with high radiation doses present a striking problem. Of course, one cannot judge from the small number of patients who had had laryngectomy, but it seems that this regimen has a special inherent weakness, and it has therefore been abandoned. The same kind of apparently late damage to the connective tissue associated with lengthy treatment and high doses has been demonstrated in a group of women treated for mammary carcinoma.<sup>31</sup> Fowler also pointed to this rise in late complications and the concomitant decrease in the therapeutic ratio (local control/late complications).<sup>32</sup>

The high frequency of fistulae in 1978 and 1979 after the start of split-course treatment helped to prove the striking effect of metronidazole as a prophylactic antibiotic. The combination of prophylactic metronidazole and penicillin is now a standard regimen in all laryngectomies and in many other major head and neck operations.

Our study also confirms many previous findings of a strong association between tobacco smoking and the development of laryngeal cancer.

The following conclusions are drawn from our study: (1) the frequency of fistulae is radiotherapy dose-dependent; (2) the field size influences the number of fistulae; (3) few high-dose fractions of radiotherapy are injurious; and, (4) not least, metronidazole causes a dramatic fall in the number of fistulae. Our study also shows that significant simultaneous changes may counterbalance one another. As a change from continuous treatment to split-course was made the number of fistulae increased,

whereas the induction of metronidazole decreased the number of fistulae.

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