

Advanced tracheal carcinoma – a therapeutic significance of HDR brachytherapy in palliative treatment

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The purpose of this study was to determine the benefit of high dose rate endotracheal brachytherapy as an exclusive palliative treatment of obstructive tracheal cancer.

Thirty-five patients with advanced tracheal carcinoma were treated between May 1999 and March 2001 in Greatpoland Cancer Center. They were qualified for brachytherapy due to life-threatening situations. Fourteen patients were irradiated using three fractions 7.5 Gy each one every week, six patients received three fractions 10 Gy each one every week and fifteen patients received one fraction of 10 Gy. Survival time was compared with chosen clinical factors (age, sex, Karnofsky status, tumor location, lymph nodes involvement and percent of obturation) and prescribed dose.

The median survival (Kaplan-Meier) for all patients was 6.6 months. Patients with an endoscopically controlled complete remission 4 weeks after the treatment had a significantly better survival in comparison to patients with a partial remission or no change of tumor size ($p=0.0003$). Univariate analysis revealed significant difference between patients with Karnofsky score equal with 60 or lower (28/35, 80%) and higher than 60 (7/35, 20.0%) ($p=0.005$). Difference between the grade of tumor obturation (more than 60% of tracheal lumen (27/35, 77.1%), 60% or lower (8/35, 22.9%)) was found in univariate analysis ($p=0.04$).

In multivariate analysis statistically important prognostic factor for survival was Karnofsky score ($p=0.04$). Statistical analysis revealed no differences in survival according to sex and age ($p=0.43$ for age, $p=0.19$ for sex), tumor localization ($p=0.13$), lymph node involvement ($p=0.48$) or fractionation scheme ($p=0.62$).

Exclusive HDR brachytherapy of advanced tracheal carcinoma was a safe palliative method of treatment and caused in many patients prolonged survival and improved quality of life. Most important prognostic factor for survival, confirmed in both univariate and multivariate analysis, was Karnofsky score.

Key words: tracheal carcinoma, HDR brachytherapy, radiotherapy, palliative treatment

Primary tracheal carcinoma is a rare malignancy of the respiratory tract, accounting for 0.1% to 0.4% of all cancers. They are insidious tumors that are often diagnosed late in their clinical course and at an advanced stage [5, 7, 11]. Because of uncontrolled local or recurrent disease, patients may have significant cough, dyspnea, hemoptysis. In many patients, these symptoms are primarily attributable to endotracheal obstruction. Efforts to relieve the obstructive process are worthwhile because patients may experience a significantly improved quality of life. However, many of these patients have a poor performance status and have

received multiple other therapies. As a result, treatment options are often limited.

Due to late onset of clinical symptoms many patients present with inoperable tumors. Laser resection (i.g. Nd:YAG) or stent placing procedures are not always available. In this situation, radiation therapy is the primary treatment modality [16, 19, 20]. Well-known approaches combine external and endoluminal radiotherapy [16, 20, 31]. The efficacy of definitive irradiation of tracheal carcinoma has rarely been reported in the literature [9, 28, 32] due to the rarity of this disease.

In the palliative treatment of tracheal cancer brachytherapy may be one of the effective methods of controlling dyspnea caused by obturation. Due to the location of the lesion inside the tracheal tube, the degree of clinical advancement, and patient's general condition, in some patients brachytherapy may be a successful treatment, which, when carried out on an out-patient basis, takes a short time and leads to a small number of early complications [20, 30, 31, 33].

In this retrospective study the clinical, radiographic and bronchoscopic records of patients treated exclusively with HDR endotracheal brachytherapy were reviewed to determine its effectiveness in patients with malignant tracheal obstructions.

Material and methods

Patients. Between May 1999 and March 2001 35 patients with primary tracheal tumors were treated with brachytherapy at the Department of Radiotherapy of Great Poland Cancer Center. It was 85.4% (35/41) of all patients with tracheal cancer treated in this period. The others were treated with external beam radiotherapy combined in three cases with chemotherapy. This study focuses on inoperable patients (eight female, twenty-seven male), who received a palliative HDR brachytherapy for endotracheal tumor. Due to life-threatening situations and not sufficient availability of linear accelerators we have chosen brachytherapy as a sole mode of treatment.

Age of patients ranged from 44 to 77 years, median 59.5 years. In all patients bronchoscopy and computed tomography (CT) were performed for histological diagnosis and for evaluation of the tumor extent. In most of cases tumor obturated more than 60% of trachea diameter (Tab. 1).

Computed tomography of the thorax revealed 27 cases (77.1%) with a lymph nodes involvement. Metastases to distant organs were not found.

The leading clinical symptoms were dyspnea (35/35, 100%), bifurcation syndrome (25/35, 71.4%), hemoptysis (9/35, 25.7%), and cough (9/35, 25.7%). Bifurcation syndrome was defined as a simultaneous presence of stridor and shortness of breath. Some patients presented with more than one symptom at diagnosis.

Methods. Following pre-medication one or two endobronchial catheters were placed in the bronchus, verified radiologically. The nasal passages were anesthetised using 10% lidocaine gel. Midazolam, 1 or 0.5 mg intramuscularly or intravenously was used for sedation, atropine 0.5 mg subcutaneously to minimize secretions. Airway anesthesia was attained with 1% lidocaine in 2- to 3-ml aliquots.

In the treatment 10 Ci of Iridium-192 was applied using an HDR-GAMMAMED 12i unit. To calculate the dose distribution an ABACUS computer program was em-

Table 1. Clinical data of patients

Clinical data	Number of patients
Age:	
≤59.5	15
>59.5	20
Sex:	
male	27
female	8
Histology:	
squamous cell carcinoma	27
adenoid cystic carcinoma	2
small cell anaplastic carcinoma	2
unclassified carcinomas	4
Location:	
trachea	10
trachea infiltrating one of the bronchus	15
trachea infiltrating both bronchus	10
Lymph nodes involvement:	
present	27
absent	8
Obturation (%):	
≤60	8
>60	27
Karnofsky score:	
≤60	28
>60	7
Clinical symptoms:	
dyspnea	35
bifurcation syndrome	25
hemoptysis	9
cough	9
Method of treatment:	
3 x 7.5 Gy	14
3 x 10 Gy	6
1 x 10 Gy	15

ployed. The dose was prescribed at 10 mm distance to the surface of the source (reference point). The target volume included the tumor visualized by bronchoscopy and proven by biopsy plus 2 cm safety margins in cranial and caudal direction. In all patients, the applications were performed with a 1.8 mm bronchus applicator (length 1300 mm), which was inserted endoscopically before treatment.

Fourteen patients received three fractions of 7.5 Gy, three fractions of 10 Gy were given to six patients and fifteen patients received single fraction of 10 Gy. Single fraction was given in a case of bad performance status (Karnofsky score smaller than 60). Six patients received three fractions of 10 Gy because of extended tumor size, when the tumor obturating the bronchi by more than 80%. The treatment was applied at one-week intervals.

Remission of tumor was assessed in the fourth week after brachytherapy, then in the third, sixth and the twelfth month. The results achieved were assessed using bronchoscopy and clinical examination after the end of brachytherapy.

Partial remission (PR) was defined as a 50% reduction of

tumor volume measured by bronchoscopy. Complete remission (CR) and progressive disease (PD) were defined as no evidence of local tumor or further tumor growth of more than 25%. No remission (NR) was defined as no change in tumor size or tumor growth of less than 25%. Results were compared with chosen clinical factors (age, sex, Karnofsky status, tumor location, lymph nodes involvement and percent of obturation) and given dose.

Survival time was defined as the time from the beginning of radiation therapy to the death of the patient or to the end of the twelfth month of observation. Univariate and multivariate categorized analysis calculated with Kaplan-Meier method and log-rank, F Cox tests were performed for overall survival. Multivariate and stratified analysis was done to correct the influence of numerous pretreatment and treatment factors. For non categorized data such as age Cox's regression model were used.

Results

The median survival (Kaplan-Meier) for all patients was 6.6 months (Fig. 1). After 4 weeks the patients underwent first clinical and bronchoscopic observation rating local remission and effect of treatment. In 6 cases (17.1%) complete remission (CR), in 19 cases (54.3%) – partial remission (PR), in 9 cases (25.7%) – no remission (NR) and in one case (2.9%) progression – were achieved.

After 4 weeks of observation, in 27 (77.1%) cases improvement in dyspnea was seen and in 8 (22.9%) cases no improvement in breathing was noted.

Influence of local response on survival assessed in the 1st month after brachytherapy was analyzed. Patients with an endoscopically controlled complete remission 4 weeks after the treatment had a significantly better survival in comparison to patients with a partial remission or no change of tumor size (Fig. 2, log-rank test, $p=0.0003$).

Univariate categorized analysis revealed no differences in survival according to sex and age (log-rank test, $p=0.43$ for age, $p=0.19$ for sex). Age was grouped into two groups (equal or lower than median and higher than median age). No statistical significance for age was confirmed by non categorized analysis ($p=0.574$).

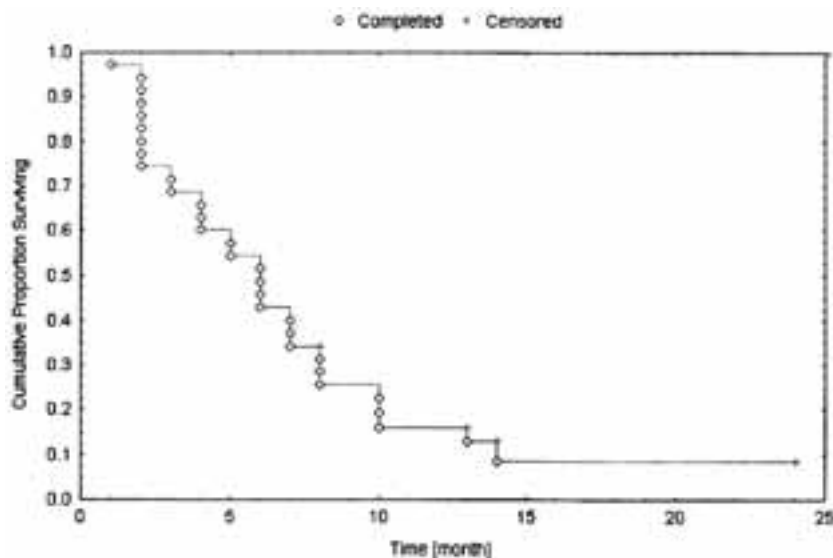


Figure 1. Surviving for all patients.

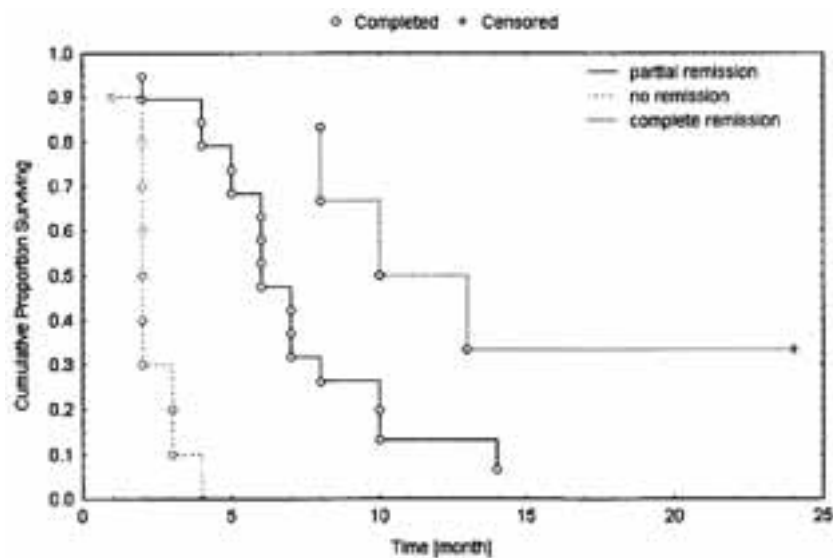


Figure 2. Influence of local response assessed in the 1st month after brachytherapy on survival (log rank test, $p=0.0003$).

Influence of tumor location on survival was analyzed. For statistical analysis patients were divided into three groups: middle and lower part of the trachea (10/35, 28.6%), lower part with infiltration of one bronchus (15/35, 42.9%) and lower part with infiltration of both bronchi (10/35, 28.6%). Tumor localization had no significant influence on survival (log-rank test, $p=0.13$).

Survival according to Karnofsky status was analyzed. Univariate analysis revealed significant difference between patients with Karnofsky score equal with 60 or lower (28/35, 80.0%) and higher than 60 (7/35, 20.0%) (Fig. 3, log-rank test, $p=0.005$).

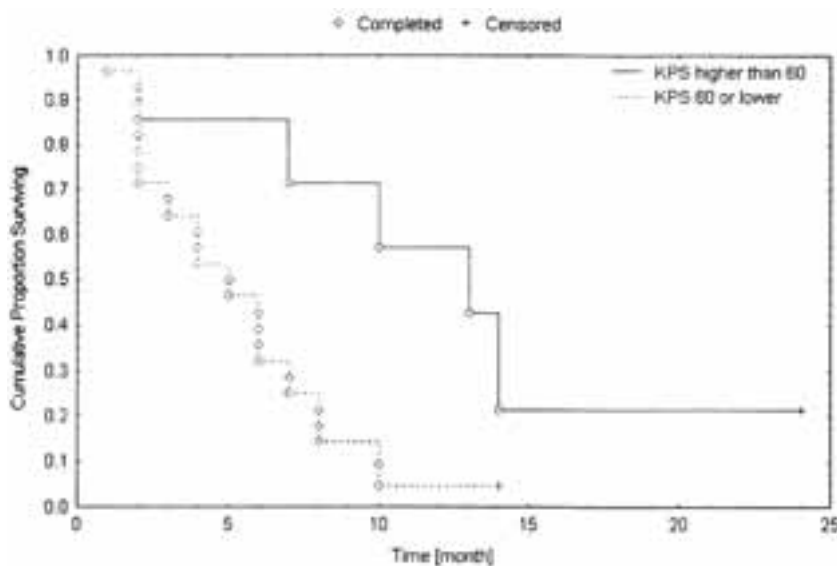


Figure 3. Survival according to Karnofsky status (log rank test, $p=0.005$).

Influence of obturation grade on survival was observed. Survival rate was significantly lower when the tumor obturated more than 60% of tracheal lumen (27/35, 77.1%) in comparison with tumors obturating 60% or less (8/35, 22.9%) (univariate analysis, log-rank test, $p=0.04$).

Patients treated with fractionation schema of three 10 Gy fractions did not show a significantly better survival than patients treated with a single fraction of 10 Gy or with three fractions of 7.5 Gy (univariate analysis, log-rank test, $p=0.62$).

Since the choice of treatment regimen exclusively depended on performance status or on the degree of obturation these factors were compared using multivariate analysis. In multivariate analysis statistically most important prognostic factor was Karnofsky score ($p=0.04$). Influence of performance status and obturation grade on fractionation schema was additionally analyzed using stratified analysis. Both factors had statistical importance only in group of patients treated with scheme – three fractions of 7.5 Gy (Karnofsky score $p=0.03$, obturation $p=0.04$).

Influence of lymph node involvement on survival was analyzed. Patients without lymph node involvement did not show better survival than patients with lymph node involvement (log-rank test, $p=0.48$).

Most frequent cause of death were local recurrence alone or with dissemination. Three patients live longer than 12 months after the end of treatment.

There were no complications during the bronchoscopy and catheter positioning. Fifteen patients (42.9%) presented with early superficial mucosal necrosis (assessed in the 1st month after brachytherapy) were successfully treated pharmacologically. In monthly repeated bronchoscopy we could observe gradual improvement in all cases with necrosis. Higher temperature and exhausting cough were

the most frequent complications. We did not observe tracheo-esophageal fistula in the whole period of observation.

Discussion

There exists no general staging system of tracheal cancer and no gender predominance is known. 50% of cases accounts for squamous-cell carcinoma and 20% to 35% – for adenoid cystic carcinoma [29]. While adenoid cystic carcinoma has a tendency to arise in the upper third of the trachea, squamous-cell carcinoma has a predilection in the lower part, including the carina. Extension beyond the trachea occurs 3 times more frequently in adenoid cystic carcinoma than in squamous-cell carcinoma [8].

Its prognosis is poor: less than 15% of patients survive more than 3 years, 40 to 90% experience local recurrence and 20 to 50% develop distant metastases [9, 14]. For extensive tracheal tumors, life expectancy ranges from 6 to 9 months; for tumors detected early, the overall survival following curative resection ranges from 0 to 60% [9, 28, 31]. Early diagnosis is uncommon, due to the lack of early symptoms and the difficulty in visualization of the tumor by routine chest x-ray. So, tracheal carcinoma has usually been diagnosed with regional spread beyond the trachea.

Before 1960, most patients were treated with endoscopic removal or limited resection, followed by external orthovoltage irradiation. Less than 15% of the patients survived more than 1 year [1, 15]. Advances in surgical procedures during the past three decades, such as the ability to fully mobilize the right hilum and pulmonary ligament, detach and reimplant the left main bronchus, perform intrapericardial dissection, and mobilize the cervical trachea have made it possible to resect tracheal carcinomas that might have previously been considered unresectable; surgery has become the most curative, however rarely feasible treatment for tracheal tumors [1, 15, 17, 23, 25]. Improvement in surgical techniques and anesthesiology over the last 3 decades has meant that surgery is now the treatment of choice in many centers with reported 5-year survivals of 20–40% for squamous cell carcinomas and 60–100% for adenoid cystic carcinomas [10, 18, 22, 34].

However, many tracheal tumors present with invasion of adjacent critical tissues or are too large to permit surgery. Operative morbidity and mortality may be significant, and only 10% of patients have tumors suitable for a curative resection.

Endoscopic resection of tracheal malignancies, laser resection, stents implantations are rapid, effective, repeata-

ble, and complementary to other treatments, although they should be considered only palliative. In our hospital this procedures are not available.

The role of adjuvant radiation therapy after an endoscopic treatment has not been clearly defined in the literature. Radiotherapy has also proven to be an efficient treatment modality for patients with unresectable or residual tumors.

In most of the reported series prior to 1970 orthovoltage irradiation was used, and not surprisingly, it was associated with significant toxicity and poor local control. There are only a few series reporting on the treatment of tracheal tumors using megavoltage irradiation [5, 7, 9].

The use of endotracheal brachytherapy has generally been limited to a palliative setting with good reports of local palliation following recurrence postprimary radiation therapy [3, 14, 24]. There are only few papers reporting results of brachytherapy after previous external beam therapy or reporting results of sole brachytherapy. Recent reports with modern high-dose radiotherapy suggest good local control and potential cure for patients with tumors confined to the trachea [6, 21, 24, 27].

PERCARPIO et al [24] reported prolonged local control with additional external beam therapy of 29.8 Gy and endotracheal brachytherapy of 23 Gy to a depth of 0.5 cm following primary irradiation 3 years prior to 47.2 Gy.

BOEDKER et al [3] also reported prolonged local control following primary irradiation 4 years prior to a dose of 60 Gy with endotracheal brachytherapy of 18 Gy to a depth of 3 mm. There were no treatment-related complications in either of these patients.

SCHRAUBE in 1994 [31] reported a median survival of 31 months in a series of 10 patients treated with external irradiation (46 to 60 Gy), followed by an endoluminal high-dose-rate brachytherapy boost in four patients. Endoscopic complete response was observed in four patients (36%), partial response in seven. In two patients, a necrotizing tracheitis with narrowing of the lumen occurred, requiring endoscopic intervention and stent implantation.

A smaller fraction size (4 Gy) was recommended to avoid toxicity.

BARAKA [2] reported a 5-year survival rate of 40% for 16 patients treated with radical dose of 52.5 Gy in 15 fractions over 21 days; three patients required tracheal dilatation for subglottic stenosis, and two others esophageal dilatation.

HARMS et al [12] described a group of seven inoperable patients with tracheal neoplasms treated with a high dose rate (HDR) brachytherapy boost (median 15 Gy, single dose 3–5 Gy) for residual tumor after external beam radiotherapy (median 50 Gy, 5x2 Gy/week). The median actuarial survival was 34.3 months. The 3-year actuarial survival rates was 32%. Local control was obtained in 5/7 patients. Late toxicity occurred in three patients (stenosis n=2, hemorrhage n=1). They concluded that a HDR brachytherapy boost was effective and feasible.

In another study HARMS et al [13] analyzed a group of 25 patients with primary tracheal carcinoma treated with external beam radiotherapy (17 squamous-cell carcinoma [SCC], 8 adenoid cystic carcinoma [ACC]). An additional HDR brachytherapy boost was carried out in 10/25 patients. The median survival for patients with SCC was 33 months (for ACC–94.2 months). The 1-, 2- and 5-year survival rates for patients with SCC were 64.7% (ACC 85.7%), 64.7% (ACC 85.7%), and 26% (ACC 85.7%). Patients with ACC and patients with a complete remission after treatment had a significantly better survival probability. Authors concluded that combined therapy was an effective treatment for primary tracheal neoplasms.

Our patients were treated in all of cases in advanced clinical stage, in bad performance status (low Karnofsky median score), what made impossible to treat them with curative intent. Due to life-threatening situations and not sufficient availability of linear accelerators we have chosen brachytherapy as a sole mode of treatment. This was a reason why we did not use external beam irradiation. Brachytherapy was performed in the same day when patient arrived to our out-patient basis.

We decided to use different treatment schema due to bad performance status of most patients.

HDR brachytherapy was well tolerated in all cases, in most patients it resulted in rapid improvement of breathing difficulties. In most cases (27/35, 77.1%) improvement in dyspnea was noted. Most frequent complication was superficial necrosis being effect of using non-centering catheter. We decided to use this catheter because of great number of highly obturated trachea, in most of cases (27/35, 77.1%) greater then 60% of lumen diameter.

Complete remission observed in the first month after the treatment was the most important prognostic factor for prolonged survival. Others significant correlations were found between survival and Karnofsky score and grade of tracheal obturation. Most important prognostic factor for survival, confirmed in both univariate et multivariate analysis, was Karnofsky score. It seems, that good performance status is more important for patients with tracheal cancer then others clinical factors like age, sex, tumor location and presence of lymph nodes metastases. HDR brachytherapy improved quality of life in most of the patients and frequency of complications was acceptable. Prospective multicenter studies are needed to determine the optimal brachytherapeutic approach.

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