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Radiotherapy in the Treatment of Stage III-IV Hypopharyngeal Carcinoma

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Abstract. *Background: The aim of this study was to evaluate the role of radiation therapy alone, employing standard fractionation, in stage III-IV hypopharyngeal carcinoma. Materials and Methods: Fourteen (38.9%) stage III and 22 (61.1%) stage IV patients with hypopharyngeal carcinoma were submitted, with curative intent, to exclusive radiotherapy to the primary tumor and regional draining lymph nodes, level II, III, IV, V and VI. Total dose ranged from 68 to 72 Gy. Results: The 5-year overall survival (OS) and disease-specific survival (DSS) rates were 15.6% and 28.1%, respectively. Five-year OS in stage III and IV patients was, respectively, 33% and 5% (p=0.028) and DSS was, respectively, 50% and 16% (p=0.029). Five-year OS and DSS rate in N0 versus N+ patients were respectively 37.5% and 75% versus 8.3% and 12.5% (p=0.07 and p=0.05). Conclusion: Overall survival at 5 years for III-IV hypopharyngeal tumor treated with radiotherapy alone is poor. It is possible that the addition of the best radiation fractionation to the best concurrent chemotherapy may improve the results, with acceptable toxicity.*

Hypopharyngeal cancer is relatively rare; in the United States in 1997 approximately 8890 new cases were reported (1). At the time of diagnosis, approximatively 60% of patients have advanced disease with cervical node metastases (2) because of the anatomic region that, when involved by cancer, does not give rise to symptoms until late. Owing to this fact and the high incidence of node metastases, the survival rate of hypopharyngeal cancer is poor and perhaps the lowest compared to other sites of the head and neck. For stage III-IV patients there is no standard treatment, but the combination of surgery, when the tumor is resectable, and radiation therapy, most often post-operative, is the favorite option. For unresectable patients, the standard treatment is radiotherapy +/- chemotherapy that may allow organ preservation.

The aim of this study was to evaluate the role of radiation therapy alone employing standard fractionation in stage III-IV hypopharyngeal carcinoma.

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Key Words: Hypopharyngeal cancer, advanced stage, exclusive radiotherapy.

Materials and Methods

From 1989 to 1998, 36 consecutive patients with stage III-IV hypopharyngeal squamous cell carcinoma were submitted to exclusive radiotherapy with curative intent at the Division of Radiotherapy of the Institute of Radiology, University "La Sapienza" of Rome, Italy.

The female: male ratio was 1.57:1 and the median age was 64 years (range 48-90 years). At the time of diagnosis, 30 patients (83%) presented weight loss >10% with respect to their usual weight. Thirty-two (88.9%) patients were early smokers (>20 cigarettes per day for >20 years) and 34 (94.4%) were early drinkers with more than 2 litres of wine per day.

Clinical presentation was dysphagia in 18 patients (50%), odinophagia in 11 (30.5%) and hoarseness in 7 (19.4%), both associated with light dysphagia. The site of origin was the piriform fossa in 25 patients (69.4%), the postcricoid area in 7 (19.4%) and the pharyngeal wall in 4 (11.1%).

All patients were submitted to clinical examination with indirect laryngoscopy and flexible endoscopic examination with biopsies under topical anaesthesia, chest X-rays, head and neck CT, blood and liver function test and MRI with gadolinium in 9 patients (25%). Thirty patients (83.3%) were considered inoperable or not suitable for intervention with acceptable quality of life by head and neck surgeons and 6 (16.7%) refused surgery. Fourteen patients (38.9%) were stage III and 22 (61.1%) stage IV. In Table I the patients are classified according to the TNM classification of the UICC 1987 (3).

After simulation with thermoplastic mask immobilization, the patients were submitted to external beam radiotherapy with 4-6 MV X-rays to the primary tumor and regional draining lymph nodes, level II, III, IV, V and VI. Parallel opposed upper neck fields, prescribed to midline and a lower neck/supraclavicular field prescribed to 3-5 cm depth, were used up to 42 Gy in 21 fractions, 2

Table I. *Clinical stage at the time of diagnosis.*

	N0	N1	N2	N3	Total
T3	6	8	3	5	22
T4	3	4	3	4	14
Total	9	12	6	9	36

Table II. *Sites of recurrences.*

	Number (%)
Primary tumor site (T)	2 (15,4)
Nodal site (N)	3 (23,1)
Distant metastasis (M)	1 (7,65)
TN	6 (46,2)
TM	1 (7,65)

Gy daily/5 days per week. After 42 Gy, the spinal cord was excluded and a bilateral posterior neck electron boost of 8 Gy was delivered in 4 fractions up to 50 Gy. An additional 18-22 Gy (median 20 Gy) up to 68-72 Gy in 9-11 fractions were added to the primary tumor site and positive nodes with 6 MV X-rays and/or 6-12 MeV electron beams: this final boost was achieved through reduced portals, with 1.0 cm margin around the original gross tumor.

Three patients (8.3%) with T3N3 stage, biopsy-proven complete remission of primary tumor and suspicion of residual disease in the lymph nodes were submitted to bilateral functional neck dissection after the end of radiotherapy.

The evaluation of tumor response was performed 4-6 weeks after the end of radiotherapy through clinical, endoscopic and CT examinations. If clinically complete remission of the primary tumor was obtained, biopsies were attempted to confirm complete remission. Tumor disappearance was considered as complete remission (CR), reduction ≥50% as partial remission (PR) and reduction <50 % as no change (NC). Further clinical and endoscopic examinations were performed every three months and CT scan every 6 months.

Survival curves were calculated from the end of radiotherapy by Kaplan-Meier method; comparison of the curves was performed by a log-rank test and a difference was considered significant if the *p* value was less than 0.05.

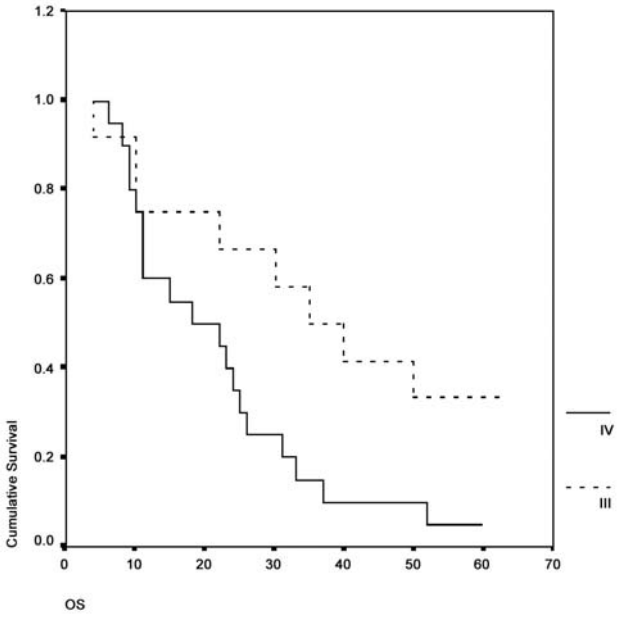

Figure 1. *OS for stage III and IV patients.*

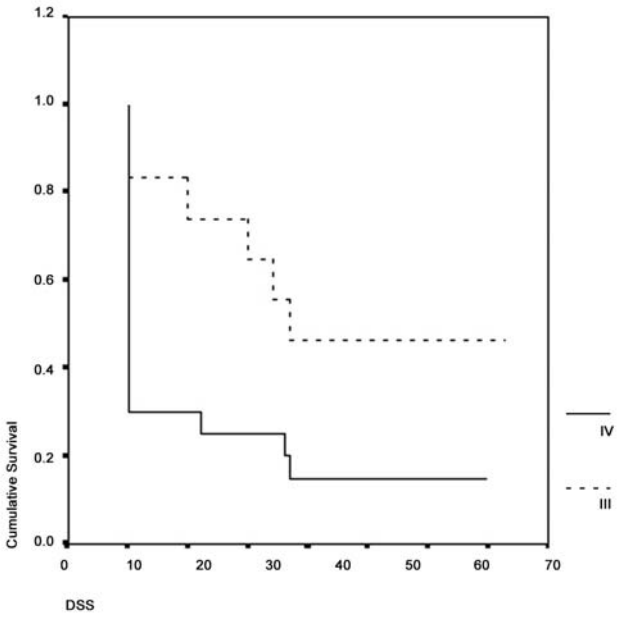

Figure 2. *DSS for stage III and IV patients.*

Results

The follow-up ranged from 4 to 63 months (median 23 months). Thirty patients (83.3%) died; 26 of these from disease, 2 from second malignancies and 2 from cerebral-vascular ictus.

The 5-year overall survival (OS) rate was 15.6% and median survival time 23 months (S.E.=4%; 95% C.I.=15-31). The 5-year disease-specific survival (DSS) rate was 28.1%.

Twenty-three patients (63.9%) obtained complete remission; among these 3 after bilateral functional lymphadenectomy, 9 (25%) partial remission and 4 (11.1%) no change. In the group of the CR, 13 (56.5%) failures were registered over a period of time ranging from 10 to 27 months (median 17 months). The sites of recurrences are shown in Table II. Five patients (38.5% of failures) were submitted to single agent chemotherapy (5-fluorouracil) with palliative intent and 8 (61.5%) had only supportive best care. All 13 patients died over a period of time ranging from 4 months to 13 months (median 7.5 months) from the diagnosis of failure. Univariate survival analysis was performed on 2 major variables: stage III *versus* IV, N0 *versus* N+. Five-year

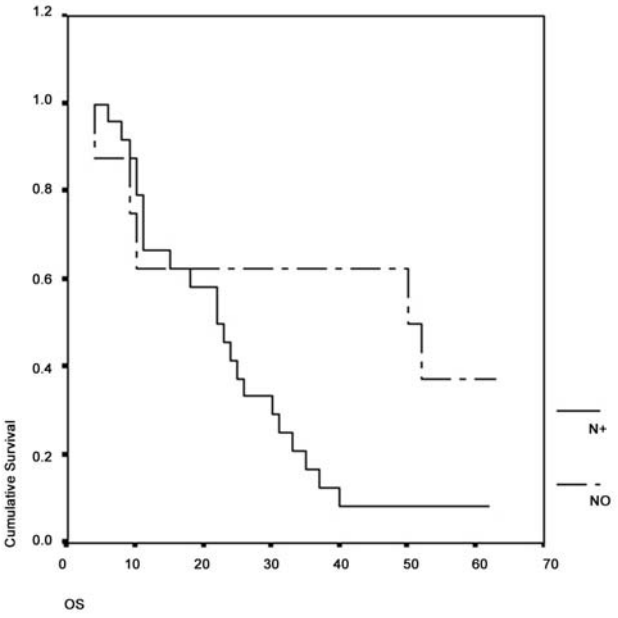

Figure 3. *OS for N0 and N+ patients.*

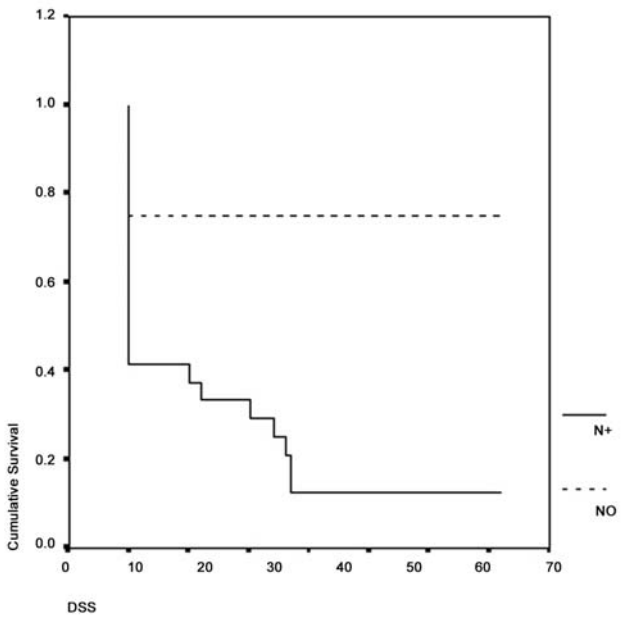

Figure 4. *DSS for N0 and N+ patients.*

OS rates in stage III and IV patients were, respectively, 33% and 5% (p=0.028) and DSS was, respectively, 50% and 16% (p=0.029) (Figures 1 and 2). Median OS was 35 months (S.E. 9; 95% C.I. 18-52) in stage III patients and 22 months in stage IV (S.E. 8; 95% C.I. 3-33).

Five-year OS and DSS rate in N0 *versus* N+ patients were, respectively, 37.5% and 75% *versus* 8.3% and 12.5% (p=0.07 and 0.05). Median OS was 50 months in N0 patients (S.E.=30; 95 C.I.=0-108) and 22 months in N+ (S.E.=4; 95% C.I.=15-29) (Figures 3 and 4).

The T3N3 patients, submitted after radiotherapy to functional bilateral neck dissection, died at 18, 33 and 31 months, the first from loco-regional recurrence (T and N), the second from local and metastatic disease and the third only from local recurrence; of these the first two had positive and the third negative pathological specimen.

Toxicity as grade II acute mucositis was observed in 28 patients (77.8%), while grade III-IV was observed in 8 (22.2%).

Difficulty in swallowing and weight loss and/or risk of aspiration that required enteral nutrition and hospitalisation were observed in 8 (22.2%) patients: percutaneous enterogastric feeding tubes were placed in 4 (11.1%) and nasogastric feeding tubes in 3 (8.3%). Airway obstruction requiring tracheotomy was registered in 1 patient (2.7%). Thirty-four (94%) patients presented loss of taste and all low-grade xerostomia. Five patients (13.9%) required an interruption of radiation therapy for a period of 3-4 days, while only 1 (2.7%) had a 7-day interruption.

Late toxicity was considered an adverse effect that appeared at least 12 months after the end of radiation therapy. Severe neck late fibrosis was observed in 1 patient (2.7%). Using several items of the LENT-SOMA scale (4) to evaluate late normal tissue toxicity, dysphagia grade II was observed in 11 (30.6%) patients, grade III in 1 (2.7%), taste alteration grade II in 6 (16.7%), hoarseness grade II in 3 (8.3%), xerostomia grade II in 9 (25%) and grade III in 11 (30.6%).

Discussion

Although hypopharyngeal cancer (HPC) is infrequent, it is associated with a poor prognosis (5-7). This is due to the fact that the hypopharynx is a relatively low sensitive area, hard to visualize and, therefore, initial signs and symptoms may be misinterpreted. Subsequently, the tumor can reach large size with extensive cervical node metastases before diagnosis. In our series, we examined 36 patients with advanced stage disease: the results confirm the poor outcome with 5-year OS rate of 15.6% and DSS rate of 28.1%. This result compares favourably to the series of Levendag *et al.* (8) who examined 147 patients with hypopharyngeal carcinoma, treated with radiotherapy alone: the 3-year local relapse-free survival and the 5-year OS in T3-T4 patients were 18 % and 8%, respectively, thus worse than ours. However, the total dose of radiation therapy in our series was medially higher, 70 Gy *versus* 61-65 Gy of Levendag.

The standard therapy regimen for large lesions and neck metastases seems to be, when technically possible, total laryngectomy and partial or total pharyngectomy, neck dissection and adjuvant radiation therapy (9-12). In a study by Pingree *et al.* (5), which includes survival data from 695 patients sorted by treatment, the 5-year OS rate was 41% for

surgery alone, 33% for surgery and radiotherapy and 21% for radiation therapy alone. Two surgical series, by Hartley *et al.* (13) and by Chevalier *et al.* (14), showed a 5-year OS rate of 11% and 33%, respectively. These difference may be explained by a different percentage of patients with stage III and IV.

Given the poor prognosis and functional loss resulting from radical surgery, radiotherapy or radiochemotherapy are alternative treatments allowing organ preservation. The EORTC trial (1996) showed an equivalent survival rate in stage III-IV resectable carcinoma of hypopharynx for patients submitted to laryngo-pharyngectomy and postoperative radiotherapy *versus* those treated with induction chemotherapy and definitive radiotherapy.

After primary radiotherapy, recurrences may be treated by salvage surgery. However, the survival rate seems poor. Two series, published by Godball *et al.* (7) and Johanesen *et al.* (15), reported 103 and 138 patients who were treated with primary radiation therapy and salvage surgery with a 5-year OS rate of 16% and 19%, respectively. These results do not differ much from the 15.6% of our series.

The survival rate seems to be influenced by stage; in our series, 5-year OS and DSS rates were respectively 33% and 50% in stage III and 5% and 16% in stage IV. Data from Spector *et al.*, in patients with pyriform sinus carcinoma treated with a combination of surgery and irradiation, showed 5-year disease-free survival ranging from 58% to 100% in stage III patients and from 31% to 71% in stage IV (11). Bataini *et al.* (16) reported a 5-year survival rate of 26% in T1-T2 patients and 17% in T3-T4 treated with radiotherapy alone. In 209 patients with pyriform fossa cancer submitted to radiotherapy alone, Dubois *et al.* (17) reported a 5-year survival rate of 3% in T3-T4 and 11% in T1-T2, while the rates rose up to 30% and 37%, respectively, in 154 patients submitted to surgery +/- radiation therapy. Emami *et al.* (10) and Spector *et al.* (12) assessed that, for patients with advanced stage disease of the pyriform fossa and pharyngeal wall, the results of combined surgery and radiotherapy were superior to those of exclusive radiotherapy.

Cervical node metastases are a certain risk factor constituting the best prognostic indicator in patients with head and neck tumors (18). In the current series, 5-year OS and DSS rates were respectively, 37.5% and 75% in N0 patients and 8.3% and 12.5% in N+ (p=0.07 and 0.05). Owing to the progressive decrease of tumor control rate after radiotherapy alone if the number and the diameter of involved lymph nodes increase, a neck dissection (ND) has been frequently recommended after radiotherapy, particularly in N2-N3 disease (19-21). In our series, 3 patients with suspicious residual disease in the neck and complete biopsy-proven T response after radiotherapy, were submitted to functional bilateral ND:2 had residual tumor in their pathologic specimen and all manifested loco-regional and/or distant recurrence after neck dissection. Because of a clinically different rate of response in the primary site and in the regional nodes, it seems reasonable to offer a ND to those patients with complete response of the primary tumor, to improve outcome (22). Dacum *et al.* (23) submitted patients, who presented neck node partial response after induction chemotherapy and concurrent radio-chemotherapy, to ND and, if necessary, salvage surgery to the primary: 50% of the patients had negative neck specimen and survival rates were similar in the group having salvage surgery including ND compared to that having CR after chemo-radiotherapy. In a randomized phase III study of radio-chemotherapy (RCT) *versus* radiotherapy alone in resectable head and neck cancer, all patients with PR of the primary tumor and N2-N3 initial disease received surgery: no survival advantage was observed for patients with N2-N3 initial disease receiving ND (24). Grabenbauer *et al.* (22) analysed the role of ND in 142 patients, 64 of these with hypopharyngeal carcinoma, after primary chemotherapy. Out of 97 patients with complete remission of the primary tumor, 56 were offered ND, while 41 refused; positive neck specimen were found in 23% of patients, but in 54% of yN2c-yN3, in 7.5%-10% of oral cavity and oropharynx tumor and in 19% of hypopharynx. No survival improvement was found in patients with ND compared with patients without ND. A similar percentage of residual disease in the neck specimen after radio-chemotherapy in advanced head and neck disease was found in other recent series; the positivity of specimen accorded with initial N category, ranging from 36% for N2 to 50% for N3 (25, 26). However residual disease after treatment seems to be lower after aggressive new protocols, using high external beam radiation doses and concomitant chemotherapy. Wanelo *et al.* (27) reported only 22% of residual disease in the neck specimen of N1-N3 patients. Even with the lack of randomised trials to address the value of ND and the absence of proven survival advantage so far, Grabenbauer *et al.* (22) claim that ND is probably indicated in patients with hypopharygeal tumor N3 at initial diagnosis, CR of the primary tumor after radiation therapy and/or chemotherapy, and multiple persisting nodes.

Owing to the poor 5-year OS and DSS rates of series employing radiotherapy alone, it seems reasonable to associate chemotherapy to radiotherapy. The meta-analysis (28) of chemotherapy added to loco-regional treatment for head and neck squamous cell carcinoma (HNSCC) showed that concomitant radio-chemotherapy gave significant benefit corresponding to an absolute survival benefit of 8% to 5 years. However, the authors claim that heterogeneity of the trials prohibit firm conclusion, particularly the third meta-analysis including trials of larynx preservation. These trials compared the standard treatment, that is surgery plus radiotherapy, with neo-adjuvant chemotherapy followed by radiotherapy in responders or by radical surgery plus radiotherapy in non responders. There was an absolute negative effect in the chemotherapy arm, with some suggestion, derived from

EORTC trial, that chemotherapy may be beneficial only for hypopharyngeal tumor (hazard ratio 0.9). In the EORTC study, radiation therapy consisted of a conventional schedule of 70 Gy for 7 weeks at 35 fractions, 5 fraction per week, single fraction of 2 Gy. The final report of a randomized trial by Beauvillain *et al.* (29) confirmed the poor results of neoadjuvant chemotherapy; this study compared neoadjuvant chemotherapy (three courses of cisplatin and fluorouracil) plus surgery plus radiotherapy (arm A) with the same chemotherapy plus radiotherapy (arm B), in 92 patients with T3 or T4-N0,N3 hypopharyngeal carcinoma. The 5-year OS was 37% in arm A and 19% in arm B, because of a better local control rate (63% *versus* 39%). Fractionation, total dose of radiotherapy and also 5-year OS in arm B were similar to our series, despite the use of neoadjuvant chemotherapy. For non responders to chemotherapy, there was no difference between the two arms: this could be related to the fact that chemotherapy can select cells resistant to subsequent radiotherapy and consequently can select among patients with good prognosis and those with poor prognosis. However, if neoadjuvant chemotherapy is offered, survival of patients with good prognosis seems to be improved only with aggressive treatment.

For HNSCC, protraction of overall treatment time may produce a reduction in the local control probability, owing to accelerated tumor repopulation during the protracted time of treatment. Hendry *et al.* calculated an extra radiation dose of approximately 0.6 Gy for each additional day of treatment, to preserve the same level of local control using 2 Gy daily fractionation (30). In contrast to conventional radiotherapy, the accelerated protocol delivers a similar total dose in less time counteracting the tumor repopulation of clonogens during treatment without increasing late normal tissue complications. From the data of Cancer Care Ontario Practice Guideline Initiative - Head and Neck (31), of 11 randomised trials of accelerated radiotherapy *versus* conventional irradiation, 6 demonstrated a significant increase in loco-regional control in favour of accelerated radiotherapy, but only one a significant increase in overall survival. From literature data, it seems reasonable that a modest acceleration of irradiation without significant reduction in total dose, like concomitant boost (32-34), with consequently modest reduction in overall treatment time, can improve loco-regional control and, perhaps, overall survival. Staar *et al.* (35) reported a randomised study in 240 patients with stage III-IV oro- and hypopharyngeal carcinoma, using hyperfractionated-accelerated radio-chemotherapy *versus* hyperfractionated-accelerated radiotherapy: after a median follow-up of 22.3 months, the 2-year loco-regional control rate was 51% after radio-chemotherapy and 54% after radiotherapy ($p=0.14$), with no statistical difference in local control in the group of 62 patients with hypopharyngeal carcinoma. The authors came to the conclusion that the accelerated radiotherapy limits the additional benefit of concurrent chemotherapy, especially in hypopharyngeal carcinoma. Morris *et al.* (36) reported the results of accelerated superfractionated radiotherapy with concomitant boost starting from the third week of treatment and a total dose of 71.8 Gy in 39 days. For patients with tumor volume >30 cm^3, the 5-year DSS rate was 27%; the 5-year survival rate of all patients was 25%. These results seem encouraging with respect to the 5-year OS of our series treated with radiotherapy alone.

Conclusion

Overall survival rates at 5 years for III-IV hypopharyngeal tumors treated with radiotherapy alone are poor; the DSS is better compared to the overall survival, but there is an excess death rate from intercurrent events especially due to second tumors. The loco-regional control and overall survival for patients in this series compared favourably to other reports employing conventional radiotherapy alone or radiotherapy followed by salvage surgery or neoadjuvant chemotherapy plus radiotherapy; our results were slightly worse than series employing altered fractionation or concurrent radiochemotherapy. For these patients with locally advanced disease, from literature data the standard therapy today does not seem to be surgery and adjuvant radiotherapy, but concomitant chemo-radiotherapy with conventional fractionation; the results of both are substantially similar with the advantage of organ preservation in the latter. Modest acceleration of radiotherapy may be a valid alternative if the total dose is not reduced. The role of concomitant chemo-radiotherapy with altered fractionation must be yet defined; it is possible that the addition of the best radiation fractionation to the best concurrent chemotherapy will improve the results with acceptable toxicity.

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