The Prevalence and Impact of Cervical Spine Pathologies in patients with Nasopharyngeal Carcinoma

Abstract

OBJECTIVES: Nasopharyngeal carcinoma (NPC) and its treatment can lead to cervical spine pathologies such as metastases, osteoradionecrosis (ORN) and infection. However, the occurrence rate and relationship between timing of diagnosis and outcomes of the ever-advancing technology of radiation therapy is largely unknown. Hence, the aim of this study is to determine the prevalence and impact of cervical spine pathologies in patients with NPC.

MATERIALS AND METHODS: This was a cross-sectional study of all newly diagnosed cases of NPC from 2007 to 2016 at a tertiary referral oncology and spine centre with minimum 1-year post-treatment follow-up. All cervical spine pathologies, their treatment and outcomes were determined. Presentation, onset time and correlations of the cervical spine pathology with mortality and risk factors were also analysed.

RESULTS: Out of 605 cases of verified NPC cases, cervical spine pathologies were seen in 8.9% of patients. New onset neck pain was seen in 5.3%, symptomatic cervical spondylosis in 4.8%, cervical spine metastases in 2.5%, 0.8% for local tumour invasion, 0.7% each for cervical ORN and osteomyelitis, and 0.3% for radiculopathy and myelopathy. Cervical spine pathologies were associated with an increased risk (odds ratio of 2.73) in overall mortality. Cervical spine metastases, invasion, osteoradionecrosis and infection were associated with statistically significant higher risk of mortality (p=0.01-0.02).

CONCLUSION: Cervical spine pathologies in NPC patients are heterogenous but not uncommon. Neck pain is prevalent but is often benign. ORN and osteomyelitis of the cervical spine is uncommon but have large clinical implications including higher mortality with subtle presentations.

Keywords: Cervical spine pathology; nasopharyngeal Carcinoma; neck pain; prevalence.

Introduction

Nasopharyngeal carcinoma (NPC) is a relatively rare tumour with global incidence of 87,000 cases per year and accounts for 0.6% of all cancer deaths.[1] However, it is endemic in certain areas of the world including South East Asia, Micronesia and North Africa. In Hong Kong, the crude incidence is 25.1 cases per 100,000 population with 876 new cases diagnosed in 2015 alone.[2] Cervical spine pathologies in NPC can arise from the natural course of disease as seen by direct tumour invasion to the upper cervical spine or by metastasis. It can also arise from the sequelae of NPC treatment as chemo-irradiation is the mainstay treatment for NPC.[3] Complications arising as a result of radiotherapy include osteomyelitis and osteoradionecrosis (ORN) of the cervical spine which have been well documented.[4] After ORN sets in, the bone is prone to bacterial seeding due to the lack of blood supply. It also undergoes creeping substitution whereby bone resorption and subsequent pathological fracture may occur. The cervical spine is at particular risk for infection after radiotherapy or head and neck surgery. As a result of the NPC treatment, the natural lymphoid barrier is disrupted along with erosion of the nasopharyngeal wall that normally separates the heavily bacterial colonized nasopharynx from the sterile cervical spinal column.[5] These can lead to neurological compromise, pathological fracture, instability and can be fatal.[6-8]

Nowadays, improvement in radiotherapy techniques with intensity-modulated radiotherapy (IMRT) have largely replaced conventional radiotherapy.[9] In our centre, IMRT has been used since 2006. It allows for higher target dose to the nasopharyngeal tumour and cervical lymph nodes with improved conformity as compared to conventional radiotherapy. Increased spatial accuracy also reduces the dose to organs at risk such as the spinal cord and vertebral column. It has been shown to improve local disease free survival rates as well as significantly reducing late radiation-induced toxicities.[10]

With improved treatment modalities, how this affects the overall prevalence of cervical spine pathologies is unknown. In addition, its occurrence rate, subsequent treatment and impact on disease status and survival have not been elucidated. Hence, the aim of this study is to determine the prevalence of cervical spine pathologies in NPC, risk factors for their occurrence and their subsequent treatment and clinical significance.

Patients and Methods

This is an analysis of prospectively and consecutively recruited NPC cases who were newly diagnosed from 2007 to 2016 at a tertiary referral oncology and spine centre. Patients with less than one-year post-treatment follow-up were excluded from analysis. Patients' demographics, underlying NPC staging, management and mortality were recorded. Staging of NPC was according to the Tumour, Node, Metastasis (TNM) system of the International Union Against Cancer (UICC) and the American Joint Committee on Cancer (AJCC).[11] The total IMRT radiotherapy dosage (Gray) and radiological findings from MRI and PET-CT staging were also assessed. Data regarding patient age, gender, stage of disease, strength of radiotherapy treatment and duration of time after radiotherapy were regarded as possible risk factors for developing cervical spine pathologies and hence were recorded. Any cervical spine pathologies developed after the diagnosis of NPC including cervical spondylosis, cervical spinal stenosis, radiculopathy, cervical spine metastases, local invasion by tumour, ORN and osteomyelitis were recorded. The rate of neck pain occurrence was also studied along with the presenting complaints, time to onset of cervical spine pathology from initial radiation dose in years and cervical spine radiographs.

Statistical analysis

The overall mortality rate from our data was calculated per annum. Correlations between individual cervical spine pathology and mortality were performed using Chi-square and Fisher's exact tests. Univariate analysis of cervical spine pathologies with risk factors including age, gender, time from first radiotherapy dosage, stage of disease, radiotherapy dosage and fractions were analysed using Chi-square and independent t-tests. Multivariate logistic regression analysis was performed to determine risk factors of developing cervical spine pathologies and their association with mortality risk. Statistical analyses were computed using SPSS software version 25.0 (SPSS Inc., Chicago IL).

Results

There were 674 cases of NPC diagnosed during the study period. A total of 69 cases were excluded due to less than one-year of post-treatment follow-up, leaving 605 cases for analysis. Out of all patients diagnosed with NPC, there were 180 cases of mortality, 41 of which died within the first year and were excluded from the risk factor analyses. Results were not grossly underestimated due to early mortality, as only 4 out of 41 patients who succumbed within one year had cervical spine pathologies including 2 cases of cervical spine metastases, 1 case of local tumour invasion and 1 case of symptomatic spondylosis. The crude death rate from NPC was 2.7 per 100,000 / year. The average age at diagnosis was 58 years old (range: 14-96, SD±13.5) with 73.2% male predominance. The annual rate of NPC diagnosis was similar across all years during the study period as shown in **figure 1**. The breakdown of patient demographics are shown in **table 1**. Majority of the patients suffered from Stage III and Stage IVA NPC at initial diagnosis.

A total of 54 cases (8.9%) developed cervical spine pathologies. Thirty-two patients (5.3%) developed new onset neck pain. Symptomatic cervical spondylosis as seen on

radiographs were found in 29 patients (4.8%). Cervical spinal metastases from NPC were seen in 2.5% of cases (15/605). There were also five cases of local tumour invasion to the cervical spine affecting C1/2 (0.8%), 4 cases of cervical osteomyelitis (0.7%), 4 cases of ORN (0.7%), 2 cases each of cervical radiculopathy (0.3%) and cervical myelopathy (0.3%).

Neck pain developed on average 3.8 years after the first radiotherapy dose (Range: 0.2–8.5, SD±2.6). Onset times for cervical spine pathologies are shown in **table 2**. Nearly half of the patients (47%) with cervical spine metastases were found during initial diagnosis and staging. Three out of five patients with cervical spine invasion to C1 were also diagnosed upon initial locoregional staging. Infection and ORN (**Figure 2**) occurred on average 0.9 and 1.8 years after radiotherapy, respectively. However, ORN can present with delayed onset with one patient diagnosed 4.6 years after initial radiotherapy treatment.

Cervical spinal pathologies resulted in 17 new healthcare seeking episodes. These included new referrals to orthopaedic specialists, family medicine out-patient clinics, accident and emergency attendances and unplanned visits to oncology clinics. Most cases presented with neck pain (53%) with or without neck stiffness (17%). Metastases to the cervical spine were often asymptomatic with incidental finding on imaging studies in 80% of the cases. Similarly, the majority of local tumour invasion to the cervical spine were diagnosed by imaging. One case was associated with skip lesions in the cervical spine.

Patients with neck pain, and fever or non-specific numbness presented with more sinister pathologies. Two out of four cases of ORN presented with neck pain and numbness distributed to the arm with associated C1-2 erosion and basilar invagination. One case of ORN presented with neck pain and fever associated with super-imposed infection. Three out of four cases of cervical spine osteomyelitis infection presented similarly with acute neck pain and

fever or neurological deficit. Physical examination of these patients revealed a mucosal defect in the posterior pharyngeal wall.

Univariate and logistic regression analysis for risk factors including age, gender, NPC staging, time to follow-up, use of chemotherapy, and radiotherapy dosage and fractions were performed for the development of cervical spine pathologies with results shown in **table 3**. Univariate and multivariate analysis demonstrated that only the stage of NPC disease was significantly correlated with the presence of cervical spine pathologies. Cervical spine pathologies were associated with a later stage of NPC disease. Patients with Stage IV disease were 13 times more likely to suffer from a concomitant cervical spinal pathology as compared to Stage I NPC (p=0.01). These also reflect the cases of cervical spine metastases and cervical spine invasion representing more advanced disease. Due to the heterogeneity of cervical spinal pathologies, risk factor analysis was also broken down to individual cervical spine pathologies as seen in **table 2**. Neck pain development was seen to occur more commonly in females (14/162) compared to males (18/443), older age (p=0.03) and in patients with longer follow-up duration. Neck pain development was not associated with higher radiotherapy dosage nor radiotherapy fractions. Patients with neck pain had a slightly lower radiation dosage compared to those who did not develop neck pain (64.4Gy vs 66.9Gy). These risk factors were echoed in patients who developed cervical spondylosis as well. Elderly individuals were also associated with development of osteomyelitis and myelopathy (p=0.03, p=0.02). On the contrary, patients with NPC who developed local tumour invasion were found to be significantly younger by an average 13.5 years of age (p=0.03). No other statistically significant correlation was found for other cervical spinal pathologies with age, gender, stage of disease and treatment differences.

Patients with cervical spine pathologies were associated with statistically significant higher mortality risks (p=0.03) in both univariate and multivariate analysis. Logistic regression analysis showed patients with cervical spine pathology have a 2.73-fold increased risk for

mortality (p=0.02). Cervical spinal metastases, local tumour invasion, ORN and osteomyelitis were all associated with significantly higher mortality rates. Four out of five patients with local tumour invasion succumbed due to disease (p=0.02), while three out of four patients died in patients with ORN (p=0.01) and similarly with osteomyelitis (p=0.01). Twelve out of fifteen patients with cervical spine metastases succumbed during this study period with a median survival of 23 months. Cervical spine metastases were less common than metastases to the thoracic and lumbar spine and were often occurring at the end stage of disease progression with widespread spinal metastases. Out of 180 cases of mortality, 32 patients had thoracic or lumbar spinal metastases which accounted for 27% of patients who died by disease progression or complications from metastases. Isolated cervical spine metastases occurred in only four cases, while the remaining eleven had concomitant thoracic and lumbar metastases. From those eleven, seven of which had cervical spine metastases diagnosed after the onset of other axial skeletal metastases as previously mentioned. Other statistically significant risk factors associated for mortality in both univariate and multivariate analysis included advanced stage of NPC disease, male gender, increasing age and longer duration of disease reflected by follow-up time period as shown in **table 4**.

Discussion

Patients with NPC can develop a variety of cervical spine pathologies. The development of new onset neck pain in patients after the diagnosis of NPC is higher than the global prevalence of 4.9%.[12] Similarly, females were more prevalent than males in developing neck pain with a peak age of 45 years old and a decline in numbers as age progressed. Cervical radiculopathy and myelopathy remained less common in concordance with literature findings.[13, 14] Neck pain, cervical spondylosis and degenerative conditions are time

responsive with more diagnoses after longer periods of follow-up as shown from our data. Sinister conditions such as cervical osteomyelitis or ORN are rare and each accounted for only 0.7% of patients with NPC. These figures are lower than previous studies where treatment of NPC relied on 2D conventional radiotherapy. In comparison, IMRT takes advantages of CT based radiotherapy planning to sculpt the radiation dosage to a desired field and allows for modulated radiation intensity within the same field to decrease the effects on vital structures. This ultimately decreases the risk and exposure of the cervical spine and spinal cord. In Singapore, they noted a 2% rate of ORN over a ten-year period for NPC patients treated with conventional 2D radiotherapy.[4] King *et al* noted a 1% rate of ORN with all patients treated with either conventional radiotherapy and/or brachytherapy.[15] Drop in figures were echoed in a comparative study between IMRT and conventional 2D radiotherapy with a decreased 5-year rate from 2.6% to 0.5% for ORN development.[3]

Despite the improvement in techniques and decreased rate of developing bone necrosis – ORN can lead to significant morbidity and mortality. In our study, ORN, infection, local tumour invasion and cervical spinal metastases had high mortality rates. For cases of local tumour invasion and cervical spine metastases, higher mortality reflects the advanced stage of disease. However, infection and ORN both had significantly increased risk of mortality and occurred in patients on average with Stage III disease. ORN can be superimposed with infection, causing abscess formation, neurological compromise and pathological fractures.[6, 7, 16] Three out of four cases with ORN succumbed in our series. Two of those had super-imposed cervical spine infection. One case, a 65-year-old female had basilar invagination and C1/2 instability with delayed presentation of fever and neck pain. Serial MRI showed progressive bony erosion prior to decompensation. Operative intervention was offered but the patient succumbed shortly afterwards due to respiratory depression and sepsis. The other case of C1/2 ORN with superimposed infection was offered surgical intervention but declined and

succumbed due to sepsis. Out of the cases of ORN, the one who survived was a 74-year-old gentleman with progressive basilar invagination on serial imaging. He developed super-imposed infection due to mixed oropharyngeal organisms, presenting with fever and neck stiffness. He underwent surgical intervention with occipital-cervical fusion and a prolonged antibiotic course for 6 weeks. From our experience, more aggressive intervention is warranted in cases with ORN and super-imposed infection whenever surgically fit. Presentation of cervical spine pathologies are rather non-specific with neck pain and stiffness in the majority of cases. Progressive changes on serial imaging may lead to an earlier detection and alert clinicians for more active intervention as signs and symptoms before decompensation can be quite subtle. Cases may also have pharyngeal mucosal defects detectable on physical examination that can lead to seeding of infection. We advocate for simple routine clinical examination of the oral cavity to screen for pharyngeal mucosal defects. These cases should be timely referred for a surgeon's assessment and possible flap reconstruction.[5] Close collaboration with a multi-disciplinary team approach involving orthopaedic surgeons, oncologists, oropharyngeal surgeons and microbiologists are necessary for successful management of ORN and cervical spine osteomyelitis.

In the other spectrum, cervical spine metastases were less common than metastases to the thoracic or lumbar spine and tended to occur at the latter stage of disease (7 out of 11 patients). The spine is the most common site for metastases in NPC, accounting for 54-66% of all metastatic sites in imaging studies.[17, 18] Shen *et al* subdivided metastatic NPC into the number of sites and presence of spinal involvement.[18] Spinal metastases correlated with an unfavourable median overall survival, with a decrease from 41 to 15.8 months compared to non-spinal metastases. From our study, further subdivision of spinal metastases into cervical from lumbar and thoracic spinal metastases may prove to fare worse in overall survivorship.

Limitations

One of the limitations to this study is the ten-year timeframe of the study period. Cervical spine pathologies including late toxicities of radiation may develop in more delayed time periods.[5] It is also difficult to assess for any accentuated development of cervical spondylosis, myelopathy and radiculopathy without longer prospective follow-up. A population-based approach may be required for control group comparisons in the future. This study is also limited to the data from the electronic health record system. Patients may exhibit complaints of neck pain but may not alert clinicians or seek medical attention for it.

Conclusion

Cervical spine pathologies occurring after NPC diagnosis and treatment are heterogenous but not uncommon. Most are benign as cervical spondylosis is most prevalent. Severe complications like ORN and infections are rare but should be regularly screened as misdiagnosis or delayed treatment will have significant implications on higher mortality rates. Presentations of ORN and osteomyelitis can be subtle prior to decompensation and clinicians must have a high-index of suspicion with active investigation for its occurrences during follow-up. Cervical spinal metastases are less common compared to other sites of spinal metastases. However, they were found to be associated with more advanced metastatic disease.

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Figure Legends

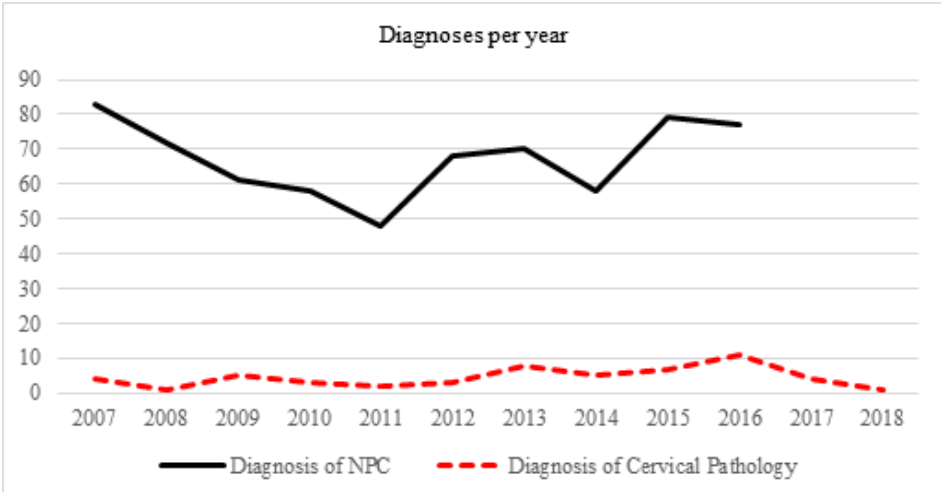

Figure 1: Diagnoses per annum. The number of naspharyngeal carcinoma (NPC) cases diagnosed per year ranged from 48 to 83 cases while cases of cervical spine pathology ranged from 1 to 11 per year. The number of NPC and cervical spine pathology diagnoses remained similar throughout the study period.

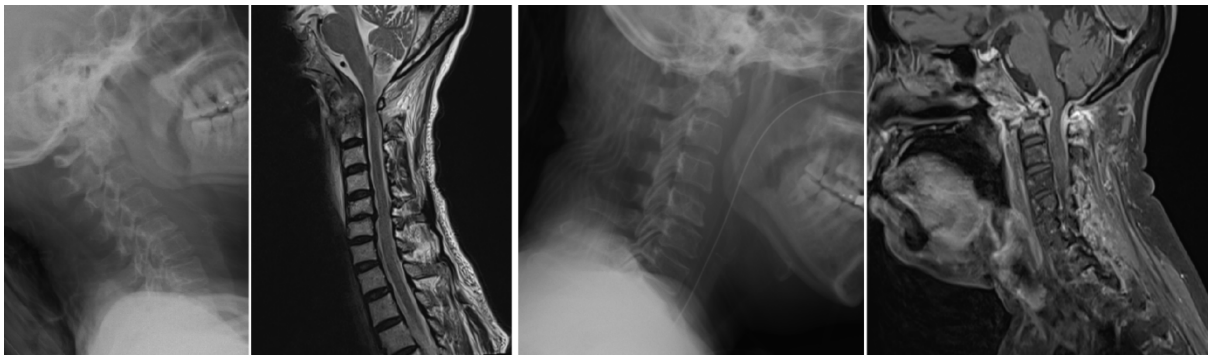

Figure 2: Patients with cervical spine pathologies after radiotherapy. Left radiograph and magnetic resonance imaging (MRI) show a patient with osteoradionecrosis. The radiograph shows sclerosis of the odontoid process and T2-weighted MRI show hypointensity of the C2. The right radiograph and MRI show a patient with C1/2 infection. The radiograph shows irregularity and collapse of the odontoid process and the T2-weighted MRI shows hyperintensities at C1/2 with collapse of the dens.

Acknowledgements: Nil

Table 1. Patient demographics

	Stage I	***Stage II***	***Stage III***	***Stage IVA***	***Stage IVB***
Male: Female	31 : 6	61 : 31	190 : 77	119 : 40	32 : 3
Age (years)	60.1 ± 12.7	62.0 ± 11.9	57.3 ± 12.9	56.5 ± 14.3	52.7 ± 14.0
Chemotherapy	10.8%	67.0%	94.4%	96.2%	97.1%
RT Dose (Gy)	66.9 ± 3.0	66.1 ± 3.9	67.3 ± 2.8	67.0 ± 6.3	66.7 ± 5.3
RT Fractions	33.4 ± 1.5	33.2 + 0.9	33.7 ± 1.4	33.4 ± 3.8	33.4 ± 2.8

RT: radiotherapy

Patient demographics according to nasopharyngeal carcinoma tumour staging. Treatment included radiotherapy with or without concurrent chemotherapy (percentage). Average radiotherapy dose and fractions are shown ± standard deviation.

Table 2. Cervical spine pathology in NPC

	No. of Cases (%)	**Average Age**			**Sex (M:F)**		**Radiotherapy Dose (Gy)**			**Radiotherapy Fractions**			**Onset After Radiotherapy (Years)**	**Time To Follow Up (Years)**		
Pathology	N=605	Yes	No	p-value		p-value	Yes	No	p-value	Yes	No	p-value		Yes	No	p-value
Neck Pain	32 (5.3%)	63.9±10.2	57.7±13.6	0.03*	18:14	0.03*	64.4±7.8	66.9±5.6	0.05*	32.0±5.0	33.4±2.8	0.03*	3.8±2.6	6.62±2.77	4.79±2.77	<0.01*
Cervical Spondylosis	29 (4.8%)	64.7±9.9	57.7±13.5	0.01*	16:13	0.02*	64.6±7.8	66.9±5.6	0.07*	32.1±4.9	33.4±2.8	0.04*	4.1±2.5	7.03±2.35	4.78±2.78	<0.01*
Cervical Spine Metastases	15 (2.5%)	56.9±13.5	58.0±13.5	0.75	12:3	0.55	66.8±3.6	66.7±5.8	0.96	33.4±1.8	33.3±3.0	0.86	1.9±3.1	2.44±1.40	4.95±2.80	<0.01*
Local Tumour Invasion	5 (0.8%)	44.6±19.8	58.1±13.4	0.03*	5:0	0.18	64.7±2.3	66.8±6.8	0.53	32.3±1.2	33.3±3.0	0.57	1.6±2.2	6.24±3.93	4.88±2.79	0.28
Osteomyelitis	4 (0.7%)	72.8±6.7	57.9±13.4	0.03*	3:1	0.94	68±2.0	66.7±5.8	0.70	33.3±0.6	33.3±3.0	0.98	0.9±0.3	1.80±0.84	4.91±2.80	<0.01*
Osteoradio-necrosis	4 (0.7%)	66.5±15.2	56.9±13.4	0.20	3:1	0.94	69±1.4	66.7±5.8	0.58	33.5±0.7	33.3±3.0	0.92	1.8±1.9	3.75±3.83	4.90±2.80	0.41
Myelopathy	2 (0.3%)	80.0±12.7	57.8±13.4	0.02*	1:1	0.46	65±1.4	66.8±5.8	0.67	32.5±0.7	33.3±3.0	0.70	2.9±2.1	5.40±5.42	4.89±2.80	0.80

Radiculopathy	2 (0.3%)	43.0±7.1	58.0±13.4	0.12	1:1	0.46	66.7±5.8	66.85.8	0.99	33.3±3.0	33.3±3.0	0.99	6.4±3.5	7.73±1.82	4.88±2.80	0.15

NPC: nasopharyngeal carcinoma; M: male; F: female

Distribution of cervical spinal pathology out of 605 patients diagnosed with NPC. Table shows averages ± standard deviation. * Significant values

Table 3. Univariate and multivariate analysis of risk factors for cervical spine pathology

		Univariate analysis		Multivariate analysis		
Risk Factors	Frequency / (% Pathology) N=54	Likelihood Ratio	p-value	Odds Ratio (95% CI)	S.E.	p-value
Stage		19.54	<0.01*			
- Stage I	2 (3.7%)	0.60	0.47	2.12 (0.38 – 11.9)	0.86	0.39
- Stage II	8 (14.8%)	0.00	0.99	1.20 (0.20 – 7.32)	0.86	0.85
- Stage III	26 (48.2%)	0.00	0.99	0.86 (0.12 – 6.18)	0.90	0.88
- Stage IV	18 (33.3%)	0.12	0.73	13.0 (1.74 – 98.0)	1.00	0.01*
Gender – Male	35 (64.8%)	2.03	0.14	0.77 (0.34 – 1.75)	0.42	0.53
Chemotherapy	45 (83.3%)	0.11	0.74	1.01 (0.31 - 3.26)	0.60	0.99
	Average (Pathology : No Pathology)	95% CI of Differences	p-value			
Age	60.8 : 57.7	-0.7 – 6.81	0.11	1.01 (0.98 – 1.04)	0.15	0.52
Time to Follow Up (years)	5.37 : 4.85	-0.3 – 1.31	0.19	1.00 (1.00 – 1.01)	0.00	0.09
RT Dose (Gy)	65.5 : 66.8	-0.6 – 3.28	0.18	1.07 (0.71 – 1.58)	0.20	0.77
RT Fractions	32.6 : 33.4	-0.2 – 1.78	0.12	0.92 (0.43 – 1.98)	0.39	0.83

R^2: 0.112. S.E: Standard Error. *: Significant values; RT: radiotherapy; CI: confidence interval

Table 4. Univariate and multivariate analysis for associations with mortality

		Univariate analysis		Multivariate analysis		
Risk Factors	Frequency (% death) N=129	Likelihood Ratio	p-value	Odds Ratio (95% CI)	S.E.	p-value
Stage		43.5	<0.01*			
- Stage I	5 (3.9%)	2.02	0.18	0.38 (0.72 – 20.7)	0.86	0.12
- Stage II	15 (11.6%)	1.97	0.12	6.70 (1.21 – 36.9)	0.86	0.03*
- Stage III	45 (34.9%)	8.59	0.04*	11.2 (1.91 – 65.2)	0.90	0.01*
- Stage IV	64 (49.5%)	17.6	<0.01*	33.6 (4.65 – 242.7)	1.00	<0.01*
Cervical Spine Pathology	21 (16.3%)	7.97	0.03*	2.73 (1.15 – 6.52)	0.44	0.02*
- Cervical Metastases	12 (9.3%)	22.9	<0.01*	-	-	-
- Tumour Invasion	4 (3.1%)	7.47	0.02*	-	-	-
- Neck Pain	7 (5.4%)	0.12	0.92	-	-	-
- Cervical Spondylosis	3 (2.3%)	3.10	0.11	-	-	-
- Osteoradionecrosis	3 (2.3%)	4.97	0.01*	-	-	-
- Osteomyelitis	3 (2.3%)	4.97	0.01*	-	-	-
- Myelopathy	1 (0.8%)	0.71	0.36	-	-	-
- Radiculopathy	1 (0.8%)	0.71	0.36	-	-	-
Gender – Male	107 (82.9%)	2.22	0.15	1.22 (0.63 – 2.37)	0.34	0.04*
Chemotherapy	109 (84.5%)	2.95	0.08	2.41 (0.95 – 6.10)	0.48	0.07
	Average (Death : No Death)	95% CI of Differences	p-value			
Age	61.1 : 57.1	1.46 – 6.56	0.02*	1.02 (1.00 –1.05)	0.01	0.04*
Time to Follow Up (years)	3.73 : 5.23	0.99 – 2.03	<0.01*	1.00 (0.99 – 1.00)	0.01	<0.01*
RT Dose (Gy)	67.2 : 64.9	0.92 – 3.65	<0.01*	0.81 (0.59 – 1.11)	0.16	0.19
RT Fractions	33.6 : 32.1	0.78 – 2.16	<0.01*	1.11 (0.59 – 2.12)	0.33	0.74

R^2: 0.286. S.E: Standard Error. *: Significant values; RT: radiotherapy; CI: confidence interval