MANAGEMENT OF THE N0 NECK IN EARLY STAGE SQUAMOUS CELL CARCINOMA OF THE ORAL TONGUE

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CERTIFICATE

I hereby certify that this dissertation on "Management of the N0 Neck in Early Stage Squamous Cell Carcinoma of the Oral Tongue" is a Bonafide work done by **Dr. V.L.Balaji,** in the Department of Surgical Oncology, College of Oncological sciences, Cancer Institute (WIA), Chennai, under my guidance and supervision, to my satisfaction.

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Date:

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AIMS AND OBJECTIVES

1. To study the incidence and patterns of cervical nodal metastases in patients clinically presenting with T1 / T2, N0 squamous cell carcinoma of oral tongue.
2. To study the various risk factors which predict the development of cervical nodal metastases.
3. To compare the survival outcomes of observation and elective neck treatment.

MATERIALS AND METHODS

A retrospective study of patients who presented with malignancies of the oral tongue treated in Cancer Institute (W.I.A) from 1995 to 2005 was done. There were 332 patients who presented with cT1/T2 N0 tongue cancers amongst 890 patients who were treated for oral tongue cancers.

Inclusion Criteria :

- All patients with biopsy proven squamous cell carcinoma and who underwent their treatment in Cancer Institute.
- Clinical T1 / T2 lesions with no palpable neck nodes

Exclusion Criteria :

- Patients with other histologies
- Patients who had undergone treatment elsewhere and presented with recurrent T1 / T2 lesions

Pretreatment evaluation consisted of a thorough history and clinical evaluation of the primary site & regional lymph nodes, a biopsy confirmation of histology and Chest Xray for metastatic evaluation.

The tongue primary was treated by brachytherapy in 288 patients. External beam radiation was used in 32 patients and surgery was done for 12 patients.

Brachytherapy was given by afterloading technique from 50 Gy to 70 Gy using $Iridium^{192}$. Teleradiation fields included the upper cervical nodes in addition to the primary. A total dose of 60 Gy was given in 32 – 34 #. Response of the primary and further management of residual or recurrent lesions was noted.

Patients were counselled about the options of neck treatment (observation vs elective neck dissection). A decision was taken by the treating physician after discussion with the patient.

The occurrence of cervical adenopathy among those patients offered only observation was noted and further management of the cervical nodes was studied in detail including timing of the appearance of nodes, treatment given and the pathologic features of the resected specimen were studied. Further recurrence patterns on followup was also noted.

Followup of these patients was updated till 2010 or their death. Patients who had defaulted during treatment or refused further treatment were also noted.

Statistical analysis was done using Pearson's chi-square test for univariate analysis and logistic regression analysis for multivariate analysis. Survival was calculated using life-tables analysis and various factors influencing survival were compared using Cox Regression analysis.

All statistical analysis was done using SPSS for Windows version 14.

BACKGROUND

Squamous cell carcinoma of the oral cavity accounts for about 30% of all cancers in India[1]. It is the second most common cancer in India[2]. This high incidence is attributed to the widespread usage of tobacco, especially oral tobacco. There is a geographical variation among the distribution, with oral cavity cancers being more common in certain parts of India[3].

The treatment requires a multimodal approach involving surgery and radiotherapy. Currently chemotherapy also is becoming an integral component of the treatment regimes. The single most important prognostic factor in oral cavity carcinoma is the presence of cervical lymph nodes. The occurrence of neck nodal metastases reduces the survival by 50 % and the presence of extracapsular involvement reduces survival by another 50 %[4].

Contemporary management incorporating advanced radiation techniques, better reconstructive facilities and modern chemotherapy and targeted therapeutic drugs have resulted in better locoregional control. As the main cause of treatment failure is locoregional, the better control rates achieved by the advances in treatment is likely to translate to better survival.

WHO has classified the oral cavity into seven subsites and the oral tongue is one of them. Oral tongue carcinomas account for 35% - 40 % of all oral cavity cancers[5]. Due to the high incidence of nodal metastases, oral tongue carcinomas have a poorer prognosis compared to other subsites of the oral cavity[6]. About 30 % of tongue carcinomas present with palpable neck nodal metastases at the time of presentation[7].

Early stage tongue carcinomas (T1 / T2, N0) account for 35 % - 40 % of all tongue carcinomas[7]. In general, the local disease can be well controlled by a single therapeutic modality *viz*, either surgery or radiation alone. Due to high incidence of occult metastatic neck disease, the optimal management of the neck remains one of the most controversial areas in the field of head and neck oncology.

Despite the high incidence of these cancers in certain geographic areas, there have been very little evidence regarding the management of the neck. The options include observation or elective neck treatment.

REVIEW OF LITERATURE

Early stage tongue cancers are treated by a single modality treatment, either surgery or definitive radiation. The local control rates for both the therapeutic modalities are similar.

Radiation can be used either in the form of external beam radiation or interstitial brachytherapy. In some very small lesions involving the tip of the tongue, intraoral cone can be used to deliver high radiation doses to a confined area.

The doses used for teletherapy usually ranges from 60 – 65 Gy in 30 to 33 # .Doses used for brachytherapy range from 50 – 70 Gy. The dose rate can be either in the low dose or high dose brachytherapy. Radiation source is usually in the form of afterloading catheters using Ir^{192}.

Surgery consists of wide excision with margins of 1 cm from the tumor as detected by inspection or palpation. Based on the extent of defect created at the end of the resection, reconstruction involves many options ranging from simple primary closure to the use of microvascular free flaps.

The choice of treatment for the primary depends on various factors including institutional policy, physician preference, patient preference, availability of radiation techniques and reconstruction facilities and the expected residual morbidity following the treatment modality.

Brachytherapy preserves maximal amount of normal tissue, however tissue effects in the long term due to fibrosis occur and include irradiation of adjacent normal tissue, leading to xerostomia, fibrosis, impaired tongue mobility and altered taste sensation. Due to the high doses of radiation, soft tissue necrosis and osteoradionecrosis are also seen as sequelae.

Of factors which influence the local control in brachytherapy are the dose rate, the gross appearance of the lesion an extension to posterior third of the tongue[8,9]. Older age (> 65 years) has been associated to higher incidence of delayed local recurrences[10].

Complications of radiation including osteoradionecrosis (ORN) and severe mucositis have been reported to be around 14 % and 17 % respectively[8,9].

Surgery causes altered phonation and difficulty in swallowing, in addition to the general risks associated with anesthesia and surgery.

The local disease control rates following surgery for early stage tongue cancers have been reported to be in the order of more than 75 %[11].

The main advantage of surgery include the presence of the entire tumor specimen for pathological analysis which will consist ofgrade of the tumor, tumor status of margins, depth of infiltration, desmoplasia, muscular infiltration, perineural spread, lymphatic emboli and presence of associated dysplasia and *insitu* carcinoma which can aid in further treatment decisions.

In a direct comparison of local control rates between brachytherapy and surgery, surgery was found to be superior (95.4 % vs 84 % for T1 lesions and 93.8% vs 72.2 % for T2 lesions)[12].

However in institutes with more experience in brachytherapy, local control rates seem to be better. Local control for T1/T2 lesions have been reported to be 87% in a

series of 166 patients by Mazeron *et al*[13] treated exclusively by brachytherapy. Even a smaller series of 19 patients 94% local control was reported by Leung *et al*[14].

Low dose rate brachytherapy treatments have also reported to have 79% local control rates for T2 cancers[15]. As similar control rates can be achieved by either treatment modality[16], either of them can be preferred for treatment of the primary. Most often the institutional treatment policies dictate the treatment modality of the primary.

Cervical Nodal Metastases:

The most important prognostic factor in head and neck squamous cell carcinomas is the presence of neck nodal metastases[17-19].

Hence if comparable local control rates are achieved for the primary disease, the next main focus of treatment should be aimed to achieve good regional nodal disease control. This guarantees the maximal chance of cure and offers the chance for the best treatment outcomes.

The optimal management of clinically N0 neck has been very controversial. Among higher stage primaries (T3 / T4), the uniform recommendations have been to perform elective nodal metastases. In early stage cancers, the issue is controversial. The main reasons cited for this include the morbidity of neck dissection in the form of shoulder dysfunction, the cosmetic deformity and the small chance of mortality due to complications associated with the surgery.

The next controversial issue is with regards to the timing of neck surgery. There have been various arguments put forth for and against to elective neck treatment which will be subsequently elaborated. Weiss *et al*[20] based on their decision analysis model recommend elective treatment for the neck when the risk of occult disease is more than 20%. This has been arrived on basis of analysis of the risk versus benefit ratio, taking into account the survival gains, the morbidity of treatment and has been generally well accepted.

If the fact that the “high-risk” group needs to be treated at an early stage is accepted, it brings forth the next question of what is the best therapeutic modality to address the neck.

Mendenhall *et al*[21] have analyzed the various subsets of head and neck cancers and have classified them into various risk groups based on the incidence of occult neck nodal metastases.

Definition of Risk Groups for the Clinically N0 Neck

Group	***Estimated Risk of Subclinical Neck Disease***	***Stage***	***Site***
I low risk	<20%	T1	Floor of mouth, oral tongue, retromolar trigone, gingiva, hard palate, buccal mucosa
II intermediate risk	20% to 30%	T1	Soft palate, pharyngeal wall, supraglottic larynx, Tonsil
		T2	Floor of mouth, oral tongue, retromolar trigone, gingiva, hard palate, buccal mucosa
III high risk	>30%	T1-T4	Nasopharynx, pyriform sinus, base of tongue
		T2-T4	Soft palate, pharyngeal wall, supraglottic larynx, Tonsil
		T3-T4	Floor of mouth, oral tongue, retromolar trigone, gingiva, hard palate, buccal mucosa

The recommendations are to address the neck when there is more than 20% incidence of occult nodal metastases.

It will be seen that T1 & T2 cancers of the oral tongue come under the low and intermediate risk groups. Hence there may be some reluctance in aggressive early surgical management as upto 70% of patients will be subjected to unnecessary surgery with associated morbidity.

But as the oral tongue and floor of mouth have been considered to behave more aggressively than other oral cavity subsites, there are proponents for more aggressive treatment for these cancers.

The rationale for elective neck treatment is on the following basis. It is known that there is a definitive incidence of occult nodal metastases in the clinically negative neck. Rationale of elective neck treatment is to address these necks early in the course of the disease to achieve best therapeutic benefit.

If the neck is observed, these occult nodal metastases enlarge so as to become clinically evident at a later date. In addition, they also demonstrate extracapsular infiltration and spread to other nodes and other distant sites, thereby lessening the chances of cure.

The incidence of occult nodal metastases in T1/T2 tongue cancers during elective neck dissection of cN0 necks have been reported variably from 14% to 61%[22,23]. The incidence of neck failures in similar patients have been reported from 14% to 49%[22,24].

As the rates of occult metastases and recurrences are similar, it would be appealing to identify the necks containing occult disease and address them earlier.

Many factors and scoring systems have been studied in detail to predict the risks of occult micrometastases in the cervical nodes. Some of the well studied and reported factors are discussed below.

1) Tumor Size :

In general, higher T stages are associated with higher incidence of neck nodal metastases. Tytor *et al*[25] report the incidence rates of 14% and 37% for T1 & T2 tumors respectively. However, not all authors find similar correlation. Rasgon *et al* and Byers *et al* did not find any such association in their series[26,27].

2) Perineural invasion and Lymphatic invasion :

Brown *et al* [28] report 71% vs 30% occult disease in the presence and absence of perineural invasion. Lydiatt *et al*[29] in their study found perineural invasion to correlate with poorer local control as well.

Brown *et al* [28] report angiolymphatic invasion also as a predictor of occult metastases with 85% of neck nodal disease in its presence as opposed to 38% in its absence.

3) DNA Ploidy :

Tytor et al reports 54% occurrence of metastases compared to 19% in the presence of DNA aneuploidy[25].Another study reports aneuploidy as a poor prognostic factor and recommends using it as a factor to decide on management of the neck[30].

4) Tumor growth pattern :

Tumors with an infiltrating or ulcerated pattern on gross appearance harbour neck metastases in 48% and 39% according to Yamazaki *et al*[31]. The same authors also report 31% and 19% incidence of neck disease in tumors displaying a superficial or exophytic growth pattern respectively. Similar relation has been reported in another study also[32].

The presence of muscular infiltration and desmoplastic reaction also was a predictor of higher incidence of neck disease[24].

5) Tumor thickness :

This is a widely studied parameter and thicker lesions have been found to fare poorly as compared to thinner lesions.

- Fukano[33] *et al* : 5.9 % for upto 5mm ; 64.7% for > 5 mm.
- Brown[28] *et al* : 38% for upto 3 mm , 41% for 3 – 7 mm & 55% for > 7 mm.
- Kligerman[34] *et al* : 7% for upto 4 mm & 30% for > 4 mm.

In a series of 173 patients treated by brachytherapy, thickness of more than 8 mm had a higher incidence of nodal metastases[35]. Similarly another series of patients treated by brachytherapy found rates of 30%, 40% & 50% incidence for thickness of upto 5 mm, 5-10 mm and more than 10 mm[36]. On comparing various tumor thickness, O'Brien *et al*[37] found a cutoff of 4 mm to be of discriminative value. Also Fakih *et al*[38] from Tata Memorial Hospital recommend a cutoff of 4 mm tumor thickness to address the neck electively.

Other lesser studied but reported factors include expression of Laminin-5 & MMTP-1 by tumor cells [39], consistency of the tumor[40] and currently, genomic profiling[41].

Due to lack of a single discriminating predictive factor, systems to predict the occult disease risk using multiple factors are also available.

Sparano[42] *et al* proposed a multivariate system incorporating the following factors :

- Greater Tumor thickness
- Greater muscle invasion
- T2 stage
- Poorly differentiated histology
- Infiltrating type of growth pattern
- Lymphatic invasion.

Scoring systems incorporating histologic factors have also been devised to predict the risk and to aid in management. Some of them are:

1) Broder's Score[43]: Classifies tumors into various grades based on differentiation and keratinization. Not found to be very predictive in many later day studies.

2) Anneroth Score[44]: Grades the following on a scale of 1 to 4 to give a final score as follows.

Parameters :

- Keratinization
- Polymorphism

- Mitoses
- Inflammatory infiltration of invasive margin
- Mode of invasion at the margin.

Grade I : 5 – 10 points

Grade II : 11 – 15 points

Grade III : 16 – 20 points

3) Bryne Score[45]: Mitoses is excluded from the Anneroth score and scores are till 16 only.

4) Martinez – Gimeno Score[46]: Seven parameters are used to assign a risk score. They are

- T stage
- Intravascular invasion
- Tumor grade
- Tumor thickness
- Tumor – Host Interface
- Inflammatory infiltrate
- Perineural spread

Treatment of Neck

The options for management of the N0 neck include:

- Observation
- Elective Neck Treatment
    - Elective Neck Irradiation
    - Elective Neck Dissection

Neck Evaluation

The aim of evaluation is to identify patients with occult disease and initiate treatment for them at an earlier date. This has been advocated because of the limitations of clinical examination alone in identifying small nodal metastases.

1) **<u>Ultrasound Neck</u>**: Giancarlo *et al*[47] when comparing ultrasound with palpation found no added advantage to usage of ultrasound.

2) **<u>CT Scan</u> :** CT scan is routinely performed in the evaluation of head and neck cancers, also it is done for planning radiation. If the neck is imaged at the same time, nodes small

enough to be palpable can be picked up. Features suggestive of metastatic involvement include loss of fatty hilum, inhomogeneity, necrotic centre & perinodal stranding. Meritt *et al*[48] report a sensitivity of 83% for CT scan in evaluation of the neck.

3) PET – CT : A study revealed sensitivity rates of 70% and specificity of 82%[49].

4) Sentinel Node Biopsy : Based on initial experience from Breast cancer & melanoma, the role of sentinel node biopsy in head & neck cancers is fast emerging. Many authors have published their experiences with this modality. A recently published multi-institutional study reports a negative predictive value of 96% for this modality[50].

The lack of experience and the restricted availability may preclude widespread usage of this investigation. The disadvantages of sentinel node biopsy in head & neck cancers are that since radiation therapy is an integral part of treatment of these cancers, the normal lymphatic pathways are altered and errors may occur.

However, in general all of these modalities may not offer much advantage over clinical examination.

Observation

This is based on the fact that many N0 necks never go on to develop recurrence and elective treatment of the neck results in unnecessary treatment of this group of patients.

Justifications for this modality include:

- Avoids overtreatment of the neck in patients who have no occult nodal metastases.
- Reduces morbidity associated with surgery / radiation to the neck.
- Careful clinical followup will identify patients who will fail in the neck at an early date and they can be addressed.
- There is no detriment in survival if the neck nodes appear at a later date and neck is addressed at that time.

The criticism against this would include that as of yet, there is no reliable technique of identifying occult metastases and delays in treatment will be detrimental to outcome. Also is the fact that if patients are not compliant with their followup

schedule, the neck disease can become non-salvagable. Further argument would include that patients with clinically evident nodes necessarily undergo a radical neck dissection with its associated morbidity.

Elective Neck Irradiation

This is recommended when the primary is treated by radiation. The neck is electively radiated till 50Gy to take care of occult metastatic disease.

The rates of control of occult metastatic disease has been reported to be as high as 99% using doses of 50 Gy[51]. Mendenhall when comparing elective neck radiation against observation reported failure rates of 1.9% vs 18%[52].

Spaulding reports 95% neck control rates for elective neck radiation, compared to 38% for observation for T1N0 disease[53]. Hence the rates of neck failures can be extrapolated to 5% which compares against rates of 4% to 7% in patients undergoing elective neck dissection.

However there are very few studies which directly compare observation against elective neck radiation. A small series of 73 patients support the use of elective neck radiation[54]. Another small study from Riyadh reports better neck control rates for neck dissection against neck radiation[55].

The data on elective neck radiation has been inferential only as most of the studies are all of small numbers and have not been directly compared against other modalities.

The disadvantage of neck radiation is that due the post radiation effects, further followup of the neck is difficult. Also these patients are at risk of developing new head & neck malignancies. If the neck has already been radiated, the lymphatic pathways will be altered making treatment difficult in this setting.

Elective Neck Dissection

Of all therapeutic modalities, elective neck dissection remains the standard against which others have been compared.

This is due to the amount of pathologic information gained by surgery. This helps to identify necks at high risk of treatment failure and also adverse prognostic factors can be identified aiding adjuvant treatment choices.

Lindberg *et al* [56] based on the patterns of lymphatic drainage have established the various levels of nodal involvement in different subsites of the head & neck. Based on this seminal analysis, the concept of selective neck dissection, i.e., removal of the nodal stations likely to be involved by metastases has been proposed.

For oral cavity cancers, levels I to III have been found to be the primary drainage basin and selective neck dissection in the form of Supraomohyoid neck dissection (SOHND) has been advocated. Byers *et al* [30] have reported 16% incidence of skip metastasis to level III or IV lymphnodes and this has led people to advise extended SOHND to include level IV dissection also for oral tongue cancers.

However recent reports have suggested a much lower frequency of skip metastasis and advocate removal of level IV nodes only if level II or III nodes appear suspicious.

The following advantages have been cited for elective neck dissection :

- High incidence of occult metastases to the neck.
- If limited neck dissection is done and done by experienced surgeons, morbidity is very minimal.
- If the neck has to be exposed during surgery for the primary, neck dissection can be combined at the same time.
- It may be very difficult to offer the follow up necessary to identify the conversion of a N0 to N+ neck.
- Time delay associated in waiting for the N0 neck to become N+ will lead to regional and distant progression of the disease.
- Cure rates have been found to be decreased in the presence of multiple nodes or enlarged nodes.
- If the follow up protocol is not strictly adhered to, the neck node may become large enough and become unsalvageable.
- Information obtained by pathologic analysis of neck dissection specimen will identify high risk patients and help in further prognostication and incorporation of adjuvant treatment.

The role of neck dissection as both a staging and therapeutic manoeuvre is appreciated by the finding of adverse features on pathologic analysis. The most important features to be noted are the number of nodes involved, the levels of nodes involved, the presence of lymphovascular invasion and presence of extracapsular spread.

The presence of perinodal spread as already seen has been considered to be a very important prognosticator of recurrences. The size of the node has a bearing upon the incidence of perinodal spread, with nodes of 1 cm displaying evidence of perinodal spread in 20%, 2 cm nodes showing 50% and 3 cm or more nodes showing 70% chance of perinodal spread.

Myers *et al*[57] report decreased survival in this group, with 5 year overall survival of 73% for the pN0 group compared to 43% for pN+ group. In a subgroup analysis, they also found that pN+/ECS-ve group had 51% survival vs 29% for pN+/ECS+ve group at 5 years. Presence of extracapsular spread was also found to significantly increase rates of neck recurrence and distant metastases.

Another factor deserving special emphasis is the disparity between clinical and pathological involvement of neck nodes. The rates of occult metastatic disease was noted in 34% of necks[58]. 13% and 19% of cN0 necks had pN2 disease and perinodal spread on pathologic evaluation.

Also it was noted that there was 21% stage migration for T1 lesions and 26% for T2 lesions. The upstaging would have implications for further adjuvant treatment and prognosis.

Adjuvant radiation is indicated to the neck if more than 1 node shows metastases, node size is more than 3 cm, there is evidence of perinodal spread, perineural spread, lymphatic emboli, soft tissue deposits in the neck or multilevel nodal involvement or if there has been unplanned surgical biopsy of the neck node.

The most contested issue in the treatment of the neck is the timing of neck dissection, i.e, the role of elective versus therapeutic neck dissection on first sign of appearance of neck nodes clinically.

Arguments put forth for therapeutic neck dissection are that survival in that population is not severely compromised. So far, there have been few studies which directly compare the two modalities.

1. Vandenbrouck *et al*[59]: On a group of 75 patients, he found survival rates of 49% for elective neck dissection versus 47% for delayed neck dissection.

2. Fakih *et al*[38]: Noticed better disease free & overall survival in patients undergoing elective neck dissection, cite that when thickness of invasion is more that 4 mm, elective neck treatment is warranted.

3. Kligerman *et al*[34]: Noticed 72% survival against 49% survival for therapeutic versus elective neck dissection.

4. Anthony Yuen *et al*[60]: No difference in survival was seen.

Most of the series have used surgery as the primary treatment modality for the primary. Even series which use radiation for the primary report better survival rates amongst patients undergoing elective neck dissection.

In a group of 233 patients[61] elective neck dissection was found to have better outcomes than therapeutic neck dissection. Haddadin *et al*[62] also report better survival for patients undergoing elective neck dissection.

However, the issue of timing of neck dissection has never been really settled. Anil D'Cruz *et al*[63] recently reporting their analysis on a group of 349 patients found that there was insufficient evidence to conclude that one treatment was better that the other.

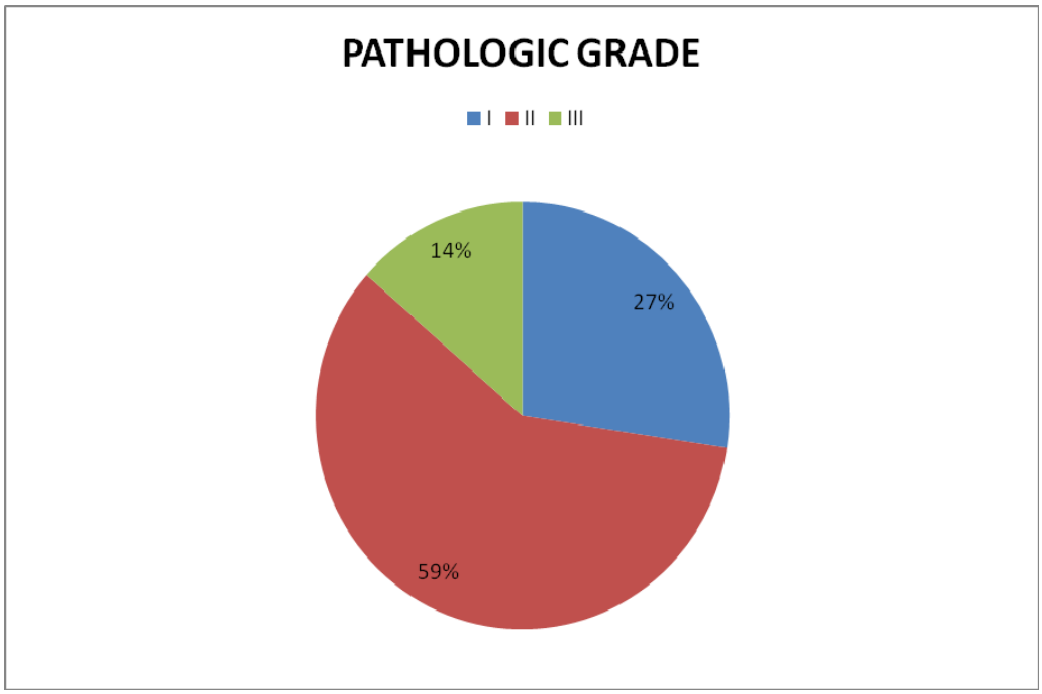
Contralateral Neck Nodes

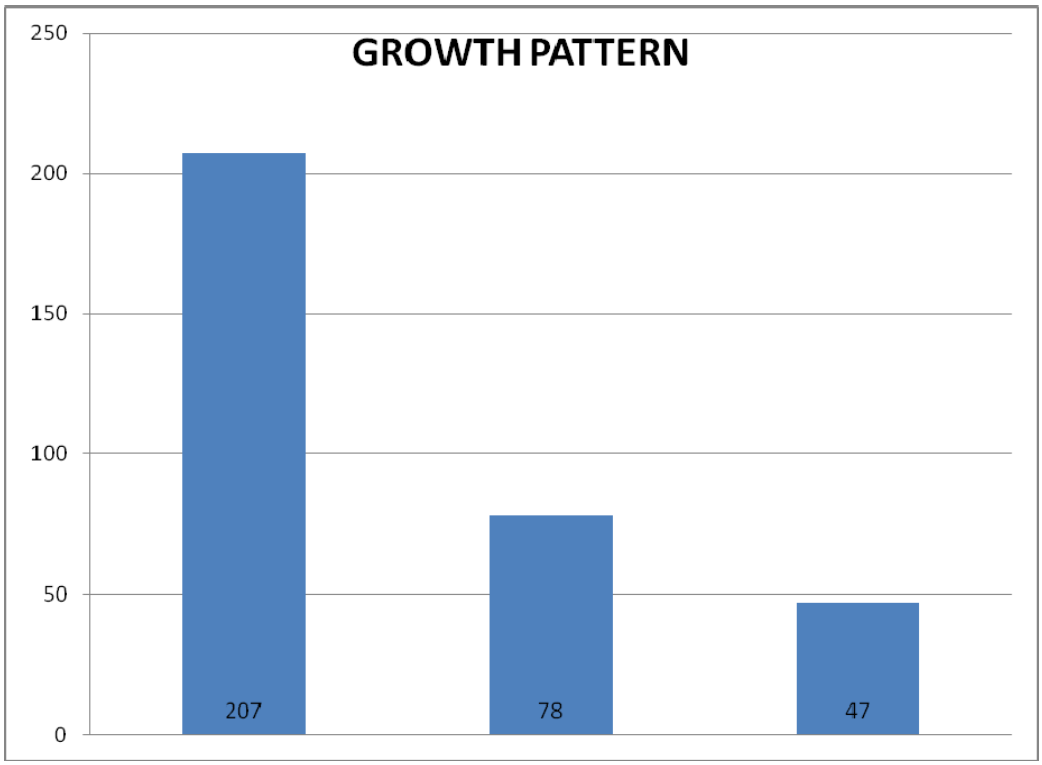
The incidence of contralateral neck nodal metastases has been reported to be in the range of 4% to 6%[64,65]. Risk factors noted have included lesions involving tip of the tongue, lesions crossing the midline, previous neck radiation or neck dissection. The incidence is very low to warrant elective treatment for the same.

RESULTS

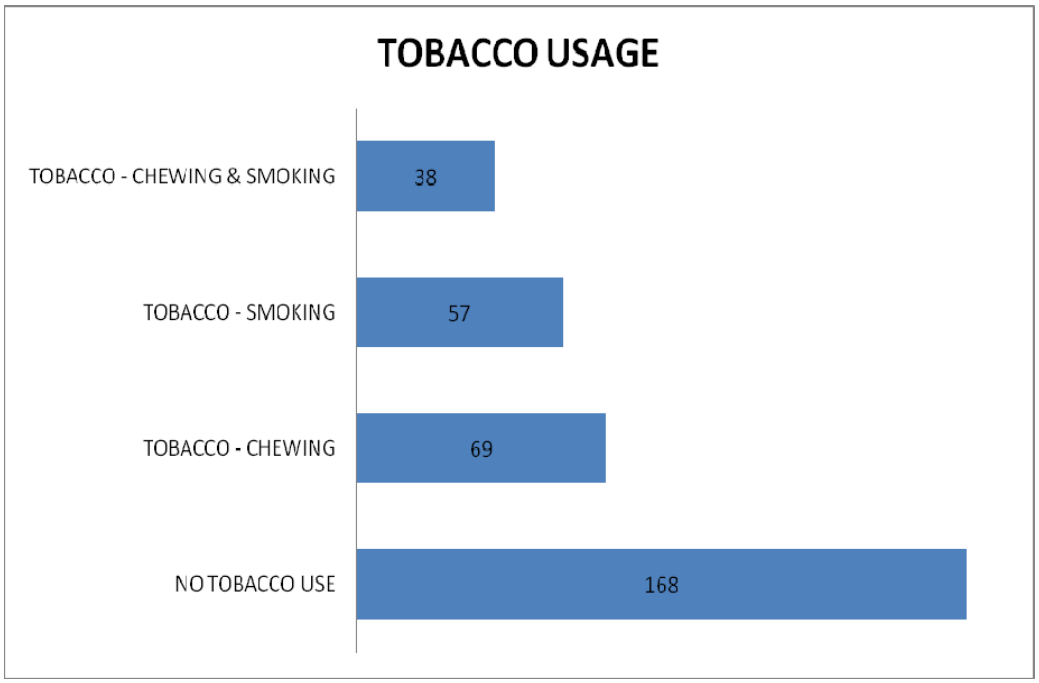
PATIENT CHARACTERISTICS

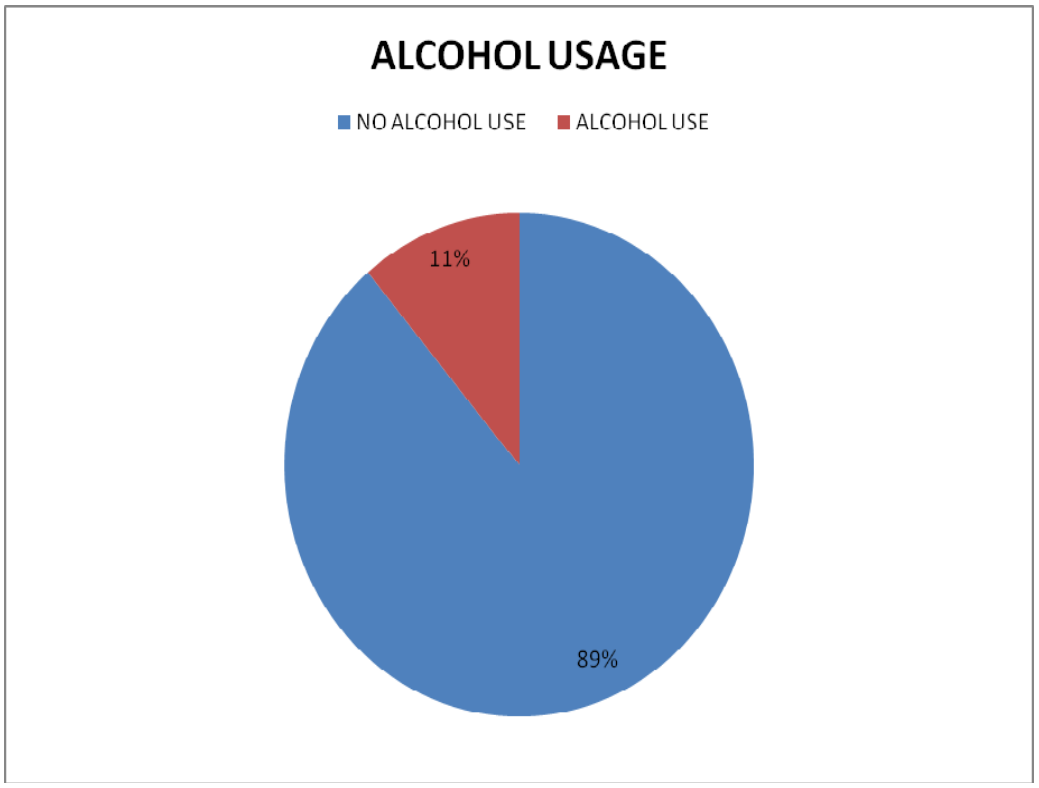
STAGE	T1 : 184 (55.4 %) T2 : 148 (44.6 %)
MEDIAN AGE (RANGE)	54 years (24 – 84 years)
MEDIAN SIZE (RANGE)	2 c.m (0.5 – 4 c.m)
COMORBID CONDITIONS	PRESENT : 105 (31.6 %) NONE : 227 (68.4 %)
GRADE	I : 91 (27.4 %) II : 196 (59 %) III : 45 (13.6 %)
GROWTH PATTERN	INFILTRATING : 207(62.3 %) EXOPHYTIC : 78 (23.5 %) ULCERATED : 47 (14.2 %)





Infiltrating Exophytic Ulcerated


TOBACCO USAGE
TOBACCO - CHEWING & SMOKING
38
TOBACCO - SMOKING
57
TOBACCO - CHEWING
69
NO TOBACCO USE
168


ALCOHOL USAGE
NO ALCOHOL USE
ALCOHOL USE
11%
89%

MULTIVARIATE ANALYSIS OF RISK FACTORS PREDICTING NECK NODE METASTASES

RISK FACTOR	**HAZARD RATIO**	**95% CONFIDENCE INTERVALS**	**p - VALUE**
AGE GROUP			
More than 40 years	1		
Upto 40 years	1.527	0.660 – 3.531	0.327
GENDER			
Female	1		
Male	1.710	0.802 – 3.647	0.165
SITE OF LESION			
Other Sites	1		
Lateral Border	2.634	0.793 – 8.750	0.114
TREATMENT TYPE			
Brachytherapy	2.128	0.883 – 5.125	0.092
Others	1		
GRADE OF TUMOR			
Grade 1 & 2	0.607	0.223 – 1.651	1.651
Grade 3	1		

RISK FACTOR	HAZARD RATIO	95% CONFIDENCE INTERVALS	p - VALUE
STAGE			
T1	**0.348**	**0.179 – 0.677**	**0.002**
T2	**1**		
GROWTH PATTERN			
Non-Infiltrating	**0.483**	**0.660 – 3.531**	**0.031**
Infiltrating	**1**		

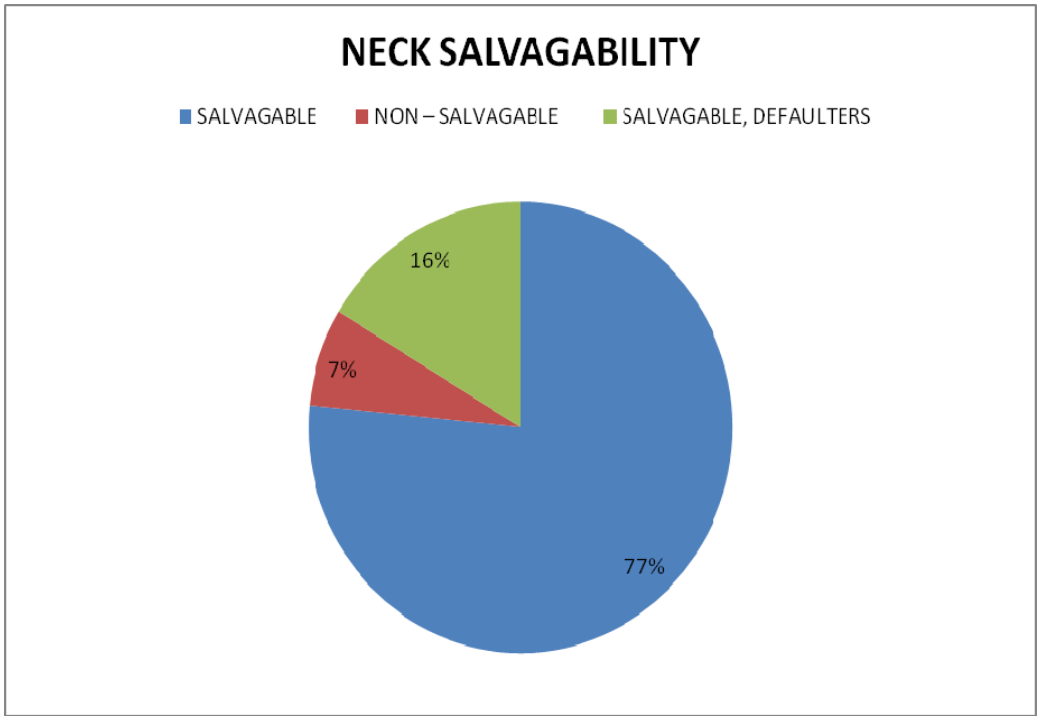
TREATMENT GROUPS AND OUTCOMES

OBSERVATION ARM (n = 236)

No clinical neck failures	:	108 (45.8 %)
Clinically detected neck failures	:	128 (54.2 %)
Pathologically proven metastases	:	101 (42.8 %)

Neck Salvagability

Salvagable	:	98 (76.5 %)
Non – salvagable	:	9 (7 %)
Salvagable , but defaulted	:	21 (16.5 %)



Treatment of Neck

Neck dissection only	:	43 (33.6 %)
Neck dissection + Radiation	:	48 (37.5 %)
Radiation only	:	14 (10.9 %)
Palliative / No Treatment	:	23 (17.9 %)

Failure Patterns

Ipsilateral Neck recurrences	:	25 (19.5 %)
Contralateral Neck recurrences	:	10 (7.8 %)
Distant Metastases	:	9 (3.8 %)
New Primary	:	6 (2.5 %)

Histopathologic Features

Pathological Involvement	:	64 (70.3 %)
Multiple Nodal Involvement	:	29 (31.9 %)
Perinodal Spread	:	50 (54.9 %)

Status At Last Followup

Alive, No disease	:	124 (52.5 %)
Dead	:	89 (37.7 %)
Lost to followup	:	23 (19.7 %)

ELECTIVE TREATMENT ARM (n = 96)

Treatment of Neck

Neck dissection	:	64 (66.6 %)
Radiation only	:	32 (33.3 %)

Failure Patterns

Ipsilateral neck recurrence	:	4 (4.2 %)
Contralateral neck recurrence	:	5 (5.2 %)
Distant Metastases	:	4 (4.1 %)
New primary	:	5 (5.2 %)

Histopathologic Features

Pathologic involvement	:	13 (20.3 %)
Multiple Nodal Involvement	:	7 (10.8 %)
Perinodal Spread	:	8 (12.5%)

Status At Last Followup

Alive, No disease	:	63 (65.6 %)
Alive, With disease	:	3 (3.1 %)
Dead	:	25 (26 %)
Lost to followup	:	5 (5.2 %)

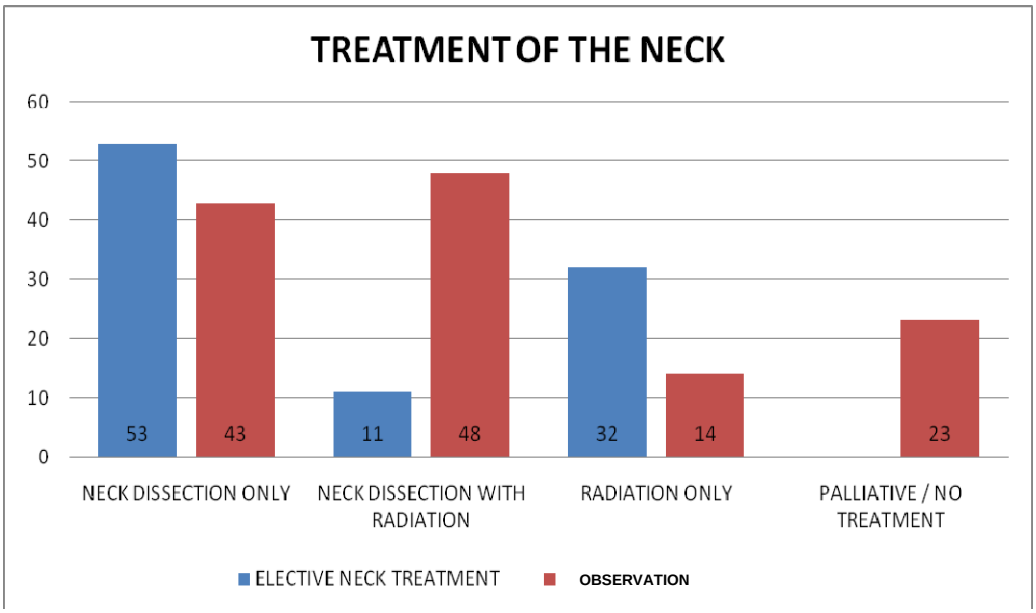
CERVICAL NODAL METASTASES

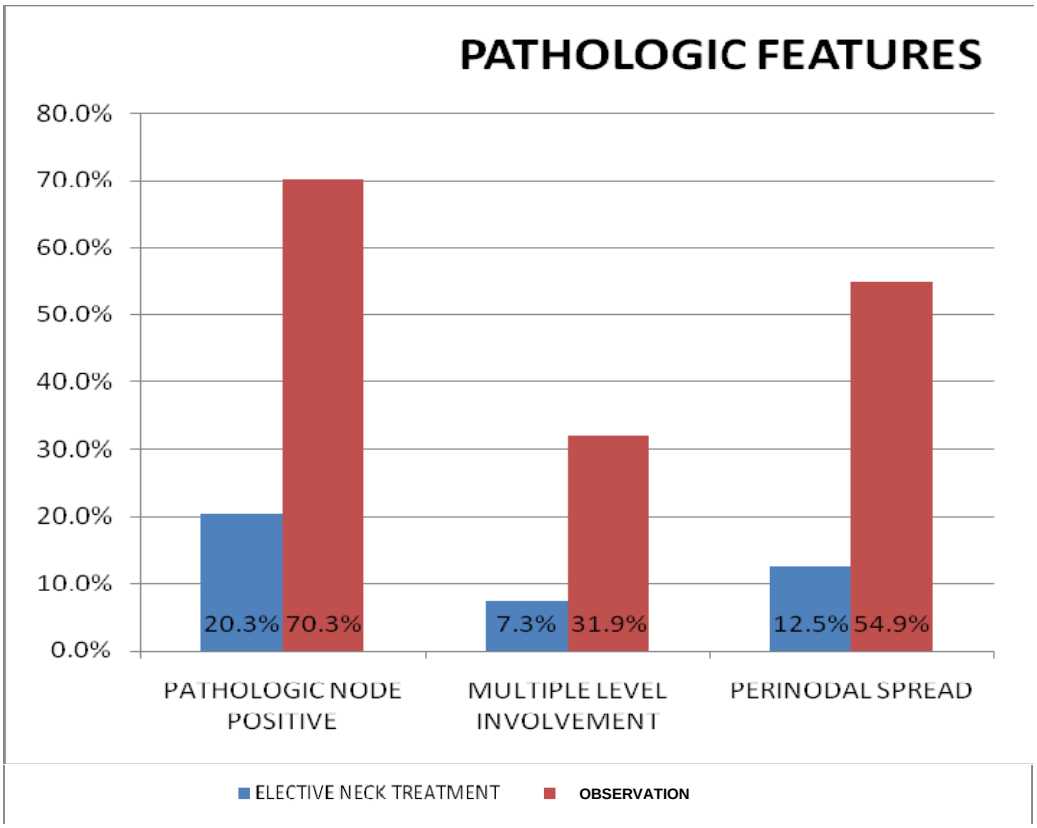
Elective Neck Dissection, n = 64

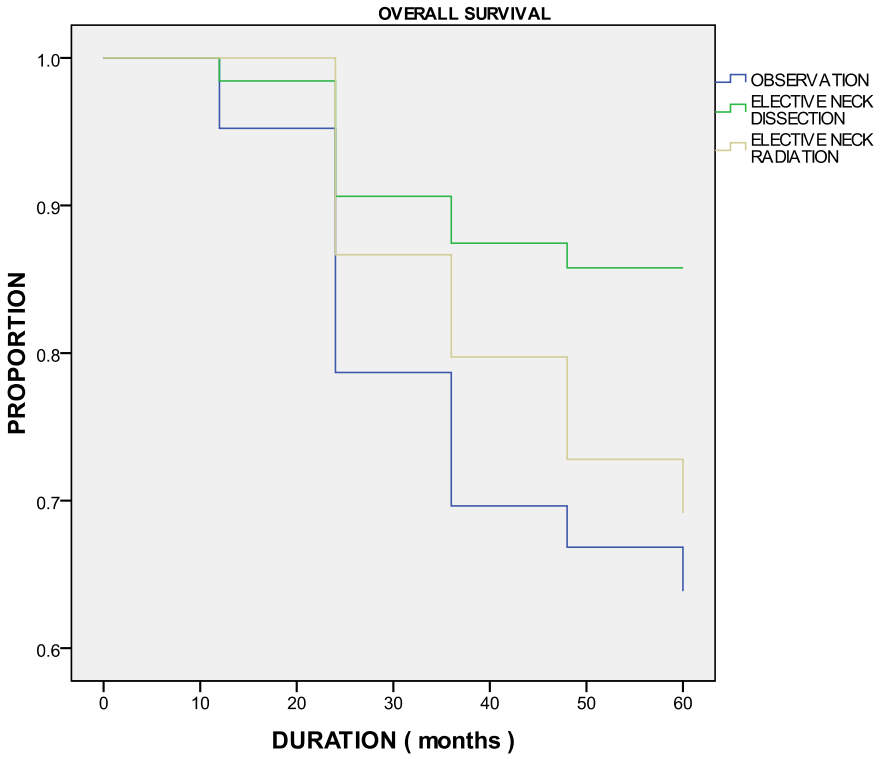
Node Positive	13 (20.3 %)
Node Negative	51 (79.7 %)
Multiple Node Involvement	5 (7.8 %)
Perinodal Spread	8 (12.5 %)

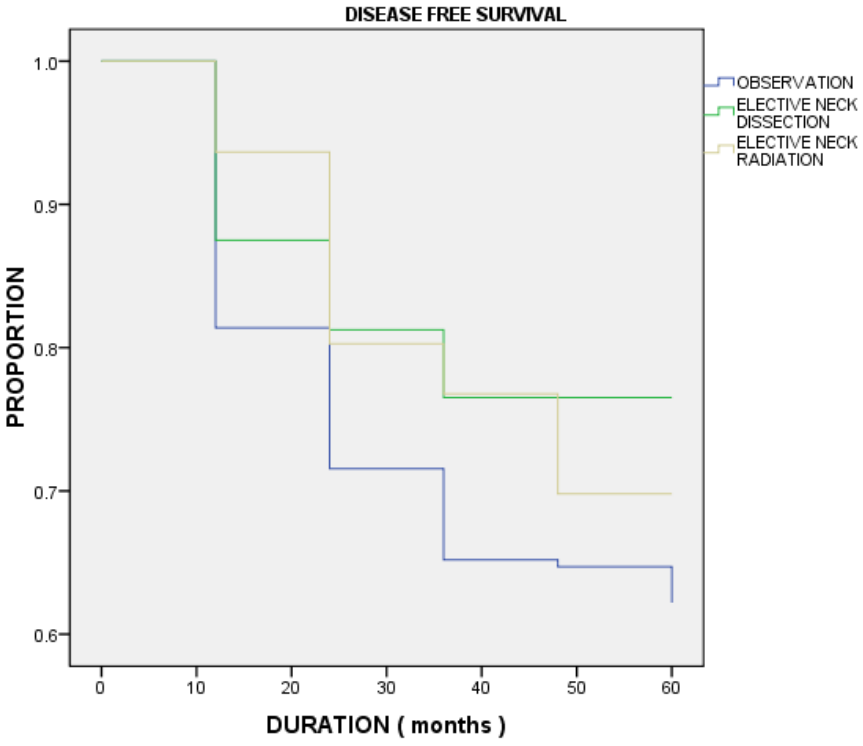
COMPARISON OF TREATMENT GROUPS

	Observation	Elective neck dissection	Elective neck radiation
Number	236	64	32
5 yr OS	64%	86%	69%
5 yr DFS	62%	77%	70%
Ipsilateral neck recurrence	101 (42.8%)	2(3.1%)	2(6.2%)
Contralateral neck recurrence	10(4.2 %)	4(6.2%)	1(3.1%)
Distant metastases	9 (3.8%)	3(4.7%)	1(3.1%)
New primary	6(2.5%)	2 (3.1 %)	3(9.4%)

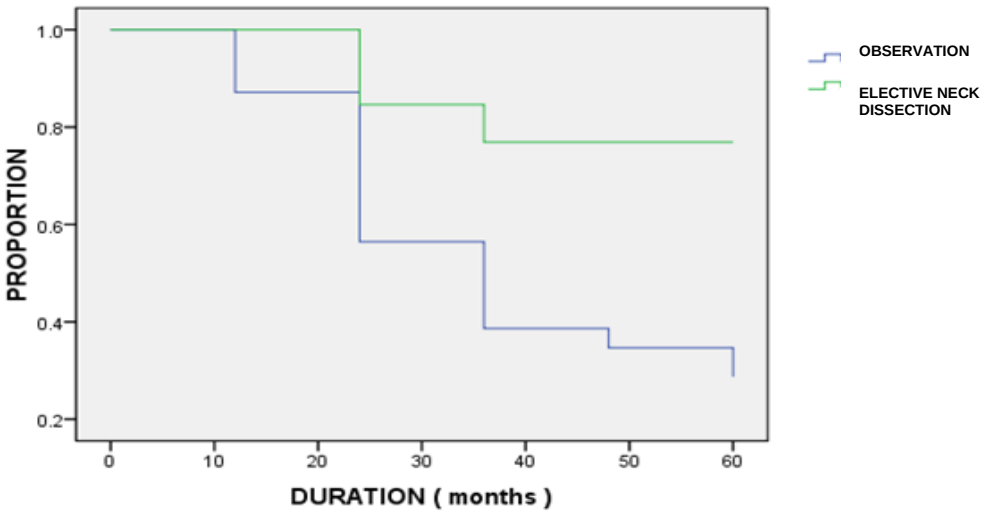

TREATMENT OF THE NECK
60
50
40
30
20
10
0
53
43
11
48
32
14
23
NECK DISSECTION ONLY
NECK DISSECTION WITH RADIATION
RADIATION ONLY
PALLIATIVE / NO TREATMENT
ELECTIVE NECK TREATMENT
OBSERVATION


PATHOLOGIC FEATURES
80.0%
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
20.3%
70.3%
7.3%
31.9%
12.5%
54.9%
PATHOLOGIC NODE POSITIVE
MULTIPLE LEVEL INVOLVEMENT
PERINODAL SPREAD
ELECTIVE NECK TREATMENT
OBSERVATION


OVERALL SURVIVAL
PROPORTION
1.0
0.9
0.8
0.7
0.6
0
10
20
30
40
50
60
DURATION (months)
OBSERVATION
ELECTIVE NECK DISSECTION
ELECTIVE NECK RADIATION

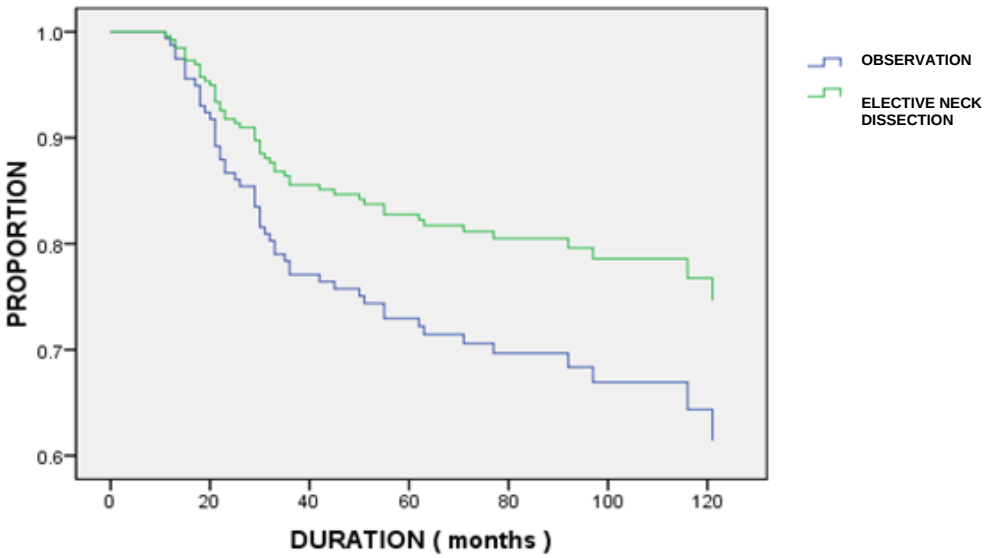

DISEASE FREE SURVIVAL
PROPORTION
1.0
0.9
0.8
0.7
0.6
0
10
20
30
40
50
60
DURATION (months)
OBSERVATION
ELECTIVE NECK DISSECTION
ELECTIVE NECK RADIATION

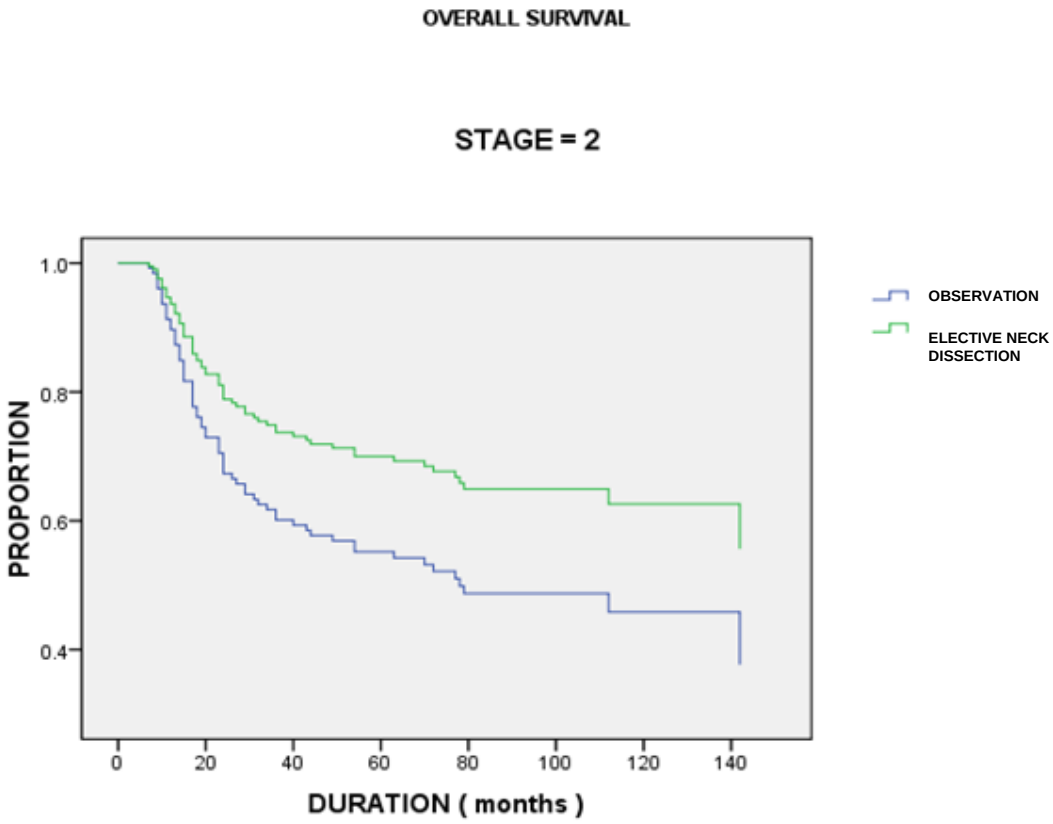
OVERALL SURVIVAL - NODE POSITIVE

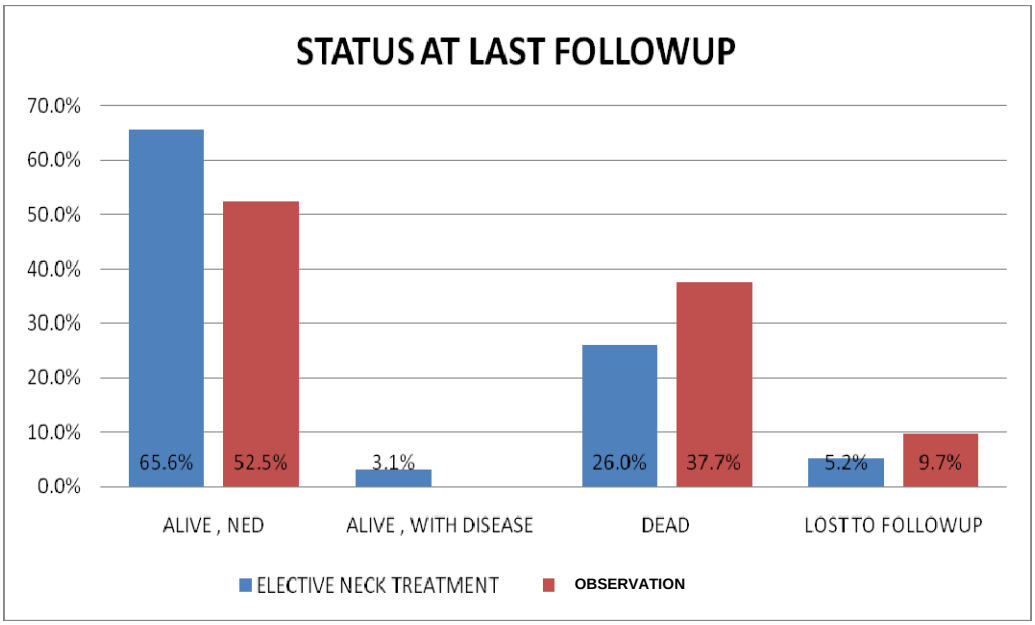


OVERALL SURVIVAL

STAGE = 1




OVERALL SURVIVAL
STAGE = 2
PROPORTION
1.0
0.8
0.6
0.4
0
20
40
60
80
100
120
140
DURATION (months)
OBSERVATION
ELECTIVE NECK DISSECTION


STATUS AT LAST FOLLOWUP
70.0%
60.0%
50.0%
40.0%
30.0%
20.0%
10.0%
0.0%
65.6%
52.5%
3.1%
26.0%
37.7%
5.2%
9.7%
ALIVE , NED
ALIVE , WITH DISEASE
DEAD
LOST TO FOLLOWUP
ELECTIVE NECK TREATMENT
OBSERVATION

DISCUSSION

OCCULT METASTASES AND CLINICAL RECURRENCES

Occult nodal metastases are metastases which are not clinically evident and they can be detected only after pathologic examination of the neck dissection specimen. The various incidence rates reported in literature are:

SERIES	**T - STAGE**	**INCIDENCE (NUMBER)**
Kowalski[24]	T1 / T2	23.1 % (n = 117)
C.J.O'Brien[66]	T1 / T2	30 % (n = 83)
S.Akthar[67]	T1 / T2	32 % (n = 94)
Decroix Y[68]	T1 / T2	34 % (n = 244)
Yuen AP[69]	T1 / T2	36 % (n = 50)
Soo-youn An[70]	T1 / T2	15.4 % / 42.9 % (n = 63)
Bourgier C[13]	T2	44.6 % (n = 279)
Vandenbrouck [59]	T1 / T2	49 % (n = 36)
Jang[22]	T1 / T2	61 % / 69 % (n = 69)
Present	T1 / T2	20.5 % / 20 % (n = 64)

The incidence of neck nodal recurrences reported for patients offered only observation in various series are:

SERIES	**T - STAGE**	**INCIDENCE (NUMBER)**
Kurokawa [23]	T1 / T2	14 % (n = 50)
Nakagawa[71]	T1 T2	25 % (n = 151) 41 % (n = 322)
Anthony Yuen [60]	T1 / T2	30.5 % (n = 35)
Al-rajhi [72]	T1 / T2	34 % (n = 85)
Kligerman[34]	T1 / T2	42 %
Vermund[73]	T1 T2	45 % 49 %
Vandenbrouck [59]	T1 / T2	53 % (n = 39)
Present	T1 T2	38.3 % (n = 134) 61.7 % (n = 102)

The rates of occult metastases when compared to other series are found to be lower in our series. The number of clinically identified recurrences are 41 % and 71.5 % for T1 & T2 lesions for patients offered observation. However, if pathologically negative but clinically palpable nodes are excluded from analysis, the rates of actual neck failure for T1 & T2 lesions are 38.3 % & 61. 7 %.The rates of recurrences are found comparable for T1 lesions but are much higher for T2 lesions as compared to other series.

The incidence of occult metastases may represent a lower value partly due to the pathologic techniques used for analysis. If the nodes are submitted as bisected specimen, then small foci of metastases tend to be missed[50]. This tends to underestimate the actual incidence of micrometastases.

Civantos *et al*[50] report that even with 3 to 6 mm cuts on routine H & E staining, using IHC in addition to conventional stains show higher incidence of metastatic foci in the lymph nodes.

Hence, it may have been the case that if further nodal clearance and IHC studies are performed on the specimen, the rates of finding occult metastases may be higher.

The incidence of contralateral metastases was 4.5 % in our study, comparable to the reported rates of 4% to 6 %[64,65].

PREDICTIVE FACTORS FOR NODAL METASTASES

On multivariate analysis, the factors found to be significantly associated with increased risk of neck nodal metastases were the growth pattern of the primary tumor and T stage of the primary.

T1 lesions have a lesser incidence of nodal metastases and an infiltrating pattern of growth of the primary has a higher incidence of nodal metastases. This association has already been reported previously by many authors[25,31,32].

Most lesions in our study were treated by brachytherapy. Hence the other significant factors reported in various surgical series like depth of infiltration, muscular involvement, presence of desmoplastic stroma and type of infiltration could not be studied.

As it is known that local control rates are similar with either surgery or brachytherapy for early stage lesions, the treatment of primary should not be a factor in predicting the incidence of nodal metastases. This was found to be the case in our study, which revealed no association between treatment of primary and incidence of nodal metastases.

Grade of the tumor, age and gender were also not found to influence the incidence of nodal metastases in our series in contrast to other series[23,30,74].

TREATMENT RESULTS

The 5 year disease free & overall survival for the treatment groups are as follows.

	GROUP	P – VALUE
Overall survival	Observation : 64 % Elective neck dissection : 86% Elective neck radiation : 69%	 < 0.01* 0.21*
Disease free survival	Observation : 62 % Elective neck dissection : 77% Elective neck radiation : 70 %	 < 0.02* 0.1*

(* Significance compared with the observation group)

As a group, the elective neck treatment group did not have a significant advantage (p=0.6), but the elective neck dissection group had a statistically significant disease free & overall survival advantage over the other two groups in our series.

Vandenbrouck *et al*[59] and Anthony Yuen[60] however found no survival advantage of elective neck dissection as compared to observation and delayed intervention. The reported survivals in various series are as follows

SERIES	ELECTIVE NECK DISSECTION (5 yr)	OBSERVATION (5 yr)
Anthony Yuen[60]	89 %	87 %
Haddadin[62]	80.5 %	44.8 %
D' Cruz[63]	60 %	60 %
Current Study	86 %	64 %
C.J.O'Brien[66] (3 year survival)	89 %	90 %
Kligerman[34] (3 year survival)	72 %	49 %

The disease free survival as reported from other series are :

SERIES	ELECTIVE NECK DISSECTION	OBSERVATION
D'Cruz[63]	68%	74%
Current Study	77%	62%
Fakih[38] (20 months)	63 %	52 %

The differences in survival could be explained by presence of adverse pathologic findings seen in patients undergoing delayed neck dissection. In the observation group, there was 31.9 % multinodal involvement and 54.9 % incidence of perinodal disease in patients undergoing delayed neck dissection. This contrasts against 20.3 % pathologic involvement, 7.3 % multinodal involvement and 12.5 % perinodal spread in patients undergoing elective neck dissection.

As all these are predictors of high recurrence rates and poor survival, this may contribute to the detriment in survival noted in this group of patients. The incidence of perinodal spread in elective neck dissection specimens as reported by other series are 13 %[68], 17% by Myers *et al*[58] and 19%[59]. The highest reported was from a series of 337 patients from Gourin[75], citing rates of 43% but many T3/T4 patients were also included in that study.

Multiple node positivity has been reported in 13%[58] to19%[60] of elective neck dissection specimens and is a factor affecting neck recurrences. Our rate was found to be lower than in other series.

Incidence of perinodal spread in clinically palpable nodes are much higher and reported rates from various series are from 43%[75] to 60%[76]. The negative impact of perinodal spread on neck and distant recurrences has already been discussed[58,59]. We had comparable rates of perinodal spread in the delayed neck dissection group.

As elective neck dissection is aimed at addressing the micrometastases at an early stage, it would be intuitive that the survival advantage conferred would be due to better control of neck disease at an early stage.

Another significant finding in our study is the higher neck salvagability rates among the observed neck group noted in our series – 76.5 %. Although Yuen[60] reports a successful salvagability rate of 100 %, other series have been unable to report such high rates. Much lower rates have been generally reported previously – 37.5 % to 62 %[77,78].

When considering salvage rates in our series it must be seen that almost 93 % of all neck recurrences were technically amenable to salvage, however actual salvage rates were lower because of patients declining further treatment. This accounted for 16.5 % of all neck recurrences and this could potentially reduce the survival rates.

The argument that waiting for neck nodes to appear clinically may result in unsalvagability does not seem to be a major problem in our study; for us the greater problem was the patient declining further treatment.

The survival rates of patients who had radiation to the neck were not significantly different from patients whose necks were observed. This may have been because patients whose tumors were large and not suitable for brachytherapy were offered only external radiation. Also the radiation portals included only the upper neck and the lower neck was not routinely addressed. Also the relatively few patients in our study may have accounted for some of the differences.

Thus from the discussion of our findings, it may be seen that elective neck dissection confers benefit for patients with N0 neck and though survival is better in this group, other factors like adverse pathologic features on neck dissection specimen and patient declining treatment may have led to poorer outcomes in the observation group.

A few significant factors seem to emerge from our analysis. The incidence of occult metastases is in the order of 20 % which is generally considered as an indication for elective

treatment and hence all T1 & T2 carcinomas of oral tongue merit elective treatment. The factors found to have significant influence of nodal metastases include the T stage and infiltrating pattern of growth.

The relative merits of elective neck dissection and observation are still contested though a benefit was conferred by elective dissection in our study. The greatest drawbacks seen in the observation arm were the higher incidence of clinically detected neck metastases and the significantly large proportion of patients refusing treatment for the same.

As most of the models predicting occult nodal metastases are described with reference to surgically treated primaries, there is paucity of such criteria for lesions treated by radiation as is the case in our institute.

With our current understanding of genetic models and other advances in molecular biology, our efforts should aim to develop predictive models for neck nodal metastases which can help us in choosing patients for elective neck treatment thus sparing the majority of other patients the morbidity of such treatment.

CONCLUSIONS

- The incidence of occult ipsilateral neck nodal metastases is around 20 % in T1 & T2 tongue carcinomas
- The rates of ipsilateral neck nodal recurrences are much higher (45 %) in patients whose necks are observed.
- The incidence of contralateral neck metastases is in the order of 5 % across all treatment groups.
- Higher T stage and an infiltrating pattern of growth of the primary were the only significant predictive factors of higher incidence of neck metastases among the factors analyzed.
- There was no survival advantage for the elective neck treatment group compared to the observation group. However patients undergoing elective neck dissection had a significantly better disease free and overall survival advantage compared to the observation group.
- Neck salvagability rate for the observation group was 76.5% in our series, though 16.5 % of all potentially salvageable patients refused treatment.
- Elective neck dissection is to be considered for treatment of all N0 necks in early tongue carcinomas.
- Better models predicting occult metastases are required to identify patients with higher incidence of neck node metastases and further randomized prospective studies comparing the treatment options are also the need of the hour.

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