Retrospective Analysis of Definitive Radiotherapy for Neck Node Metastasis from Unknown Primary Tumor: Japanese Radiation Oncology Study Group Study

Running Title

Radiotherapy for Primary Unknown Neck Tumor

Takuya Yamazaki[1], Takeshi Kodaira[2], Yosuke Ota[3], Tetsuo Akimoto[4], Hitoshi Wada[5], Junichi Hiratsuka[6], Yasumasa Nishimura[7], Shunichi Ishihara[8], Takeshi Nonoshita[9], Kazushige Hayakawa[10], Shuhei Sekii[11], Nobue Uchida[12]

[1]Department of Radiology, Nagasaki University Hospital, Nagasaki, Japan,

[2]Department of Radiation Oncology, Aichi Cancer Center, Aichi, Japan,

[3]Department of Radiation Oncology, Hyogo Cancer Center, Hyogo, Japan,

[4]Radiation Oncology Division, National Cancer Center Hospital East, Chiba, Japan,

[5]Department of Radiation Oncology, Miyagi Cancer Center, Miyagi, Japan,

[6]Department of Radiation Oncology, Kawasaki Medical School, Okayama, Japan,

[7]Department of Radiation Oncology, Kindai University Faculty of Medicine, Osaka, Japan,

[8]Department of Radiology, Toyohashi Municipal Hospital, Aichi, Japan,

[9]Department of Clinical Radiology, Graduate School of Medical Sciences, Kyushu University, Fukuoka, Japan,

[10]Department of Radiology and Radiation Oncology, Kitasato University School of Medicine, Kanagawa, Japan,

[11]Department of Radiation Oncology, National Cancer Center Hospital, Tokyo, Japan,

[12]Department of Radiation Oncology, Shimane University, Shimane, Japan

Abstract

Objective

To investigate the optimal treatment method and risk factor of neck node metastasis from unknown primary tumors (NUP) treated by radiotherapy.

Methods

Retrospective case study based on a multi-institutional survey was conducted by the Japanese Radiation Oncology Study Group. Patients pathologically diagnosed as having NUP from 1998 to 2007 were identified. Univariate and multivariate analyses of overall survival (OS), progression free survival (PFS), neck progression free survival (NPFS) and mucosal progression free survival (MPFS) were evaluated.

Results

In total, 130 patients with median age of 65 years were included. Nodal stages N1, N2a, N2b and N2c were observed for 10, 26, 43, 12 and 39 patients, respectively. All the patients received radiotherapy (RT) with neck dissection in 60 and with chemotherapy in 67 cases. The median doses to the metastatic nodes, prophylactic neck and prophylactic mucosal sites were 60.0Gy, 50.4 Gy and 50.4 Gy, respectively. The median follow-up period for surviving patients was 42 months. Among 12 patients, occult primary tumors in the neck region developed after radiotherapy. The 5-year OS, PFS, NPFS and MPFS were 58.1%, 42.4%, 47.3% and 54.9%, respectively. Univariate analysis showed that lower N stage (N1-2b), non-bulky node (< 6 cm) and negative extracapsular extension (ECE) status were the factors associated with favorable OS, PFS, NPFS and MPFS. Radical surgery proved to be a favorable factor of OS, NPFS and MPFS. On multivariate analysis, lower N stage and negative ECE status were correlated with improved survival.

Conclusions

Lower nodal stage and negative ECE status showed a favorable impact on survival and disease control in patients with NUP treated by radiotherapy.

Mini Abstract

We conducted a retrospective case study based on multi-institutional survey by Japanese Radiation Oncology Study Group to assess the efficacy of radiotherapy for neck node metastasis from unknown primary tumors.

Keywords

Unknown Primary Tumors, Head and Neck Cancer, Radiotherapy

Introduction

Neck node metastasis from clinically unknown primary tumors (NUP) accounts for 2 to 7% of head and neck malignancies[1-3]. Radiotherapy for NUP is used to control both macroscopic and microscopic cervical lesions without subsequent development mucosal lesion. However, the optimal treatment method for NUP still remains unclear in some respects. The extent of radiotherapy (inclusion of contralateral cervical lymph node regions and/or mucosal region) and irradiated dosage is still controversial[3-10]. Combination of chemotherapy has been established as the standard therapy of patients with locally advanced head and

neck cancer, but the role of chemoradiotherapy for NUP has not yet been established[4,11-17]. However, it is difficult to conduct randomized or prospective studies of this disease. The European Organization for Research and Treatment of Cancer / Radiation Therapy Oncology Group conducted a randomized phase III trial to compare different radiation therapy regimens in treating NUP patients; they tried to compare the disease-free survival of NUP patients treated with selective (i.e. ipsilateral neck) irradiation vs extensive (i.e. bilateral neck, and pharyngeal and laryngeal mucosa) irradiation[30]. However, this trial was prematurely closed because of insufficient patient accrual.

The purpose of this study was to investigate the optimal treatment method and risk factor of radiotherapy for NUP by analyzing the results of a retrospective national survey of radiotherapy for NUP patients treated from 1998 to 2007, which was conducted by the Japanese Radiation Oncology Study Group (JROSG).

Materials and Methods

The Head and Neck committee of JROSG conducted the multi-institutional survey by sending questionnaires to 18 institutes in Japan for this retrospective

study. This study was performed according to the guidelines approved by the institutional review board of each institute. Patients pathologically diagnosed as having NUP (squamous cell carcinoma or undifferentiated carcinoma), who were treated by radiotherapy from 1998 to 2007, were identified. The lymph node stage was based on the UICC-TNM 7th edition. Those who had distant metastasis were excluded. The questionnaires included : age, sex, and performance status (PS) of the patients; start and end date of radiotherapy; clinical and pathological N stage; number and maximum size of metastatic lymph nodes; involved lymph node levels; pathological status (i.e. extracapsular extension); tumor markers; diagnostic methods (CT, MR, US, PET/CT, fiberscope); combined therapies (surgery and/or chemotherapy); surgical procedures and purposes (radical, semiradical, palliative, diagnostic, planned surgery); chemotherapy contents (concurrent, neoadjuvant, adjuvant, preoperative, postoperative and alternative); purpose of radiotherapy (radical and palliative); radiation method, including range and dose of clinical target volume (local, ipsilateral or bilateral neck and mucosal region); adverse effects; treatment outcome; salvage therapy; and double cancer. As for target volume, local irradiation means the irradiation only to the level of the involved nodes

and ipsilateral irradiation means the irradiation to the prophylactic levels in addition to the level of involved nodes. No central histological review was performed for this study. Toxicities were evaluated using National Cancer Institute Common Toxicity Criteria version 4.0. Severe complications were defined as those necessitating hospitalization or surgical intervention, and/or resulting in death.

Based on the survival data from the questionnaires, 5-year overall survival (OS), progression free survival (PFS), neck progression free survival (NPFS) and mucosal progression free survival (MPFS) were estimated by using the Kaplan-Meier method. OS was defined as the time from treatment initiation to death from any cause. PFS was defined as the time from treatment initiation to disease progression or death from any cause. NPFS was defined as the time from treatment initiation to neck recurrence or death from any cause. MPFS was defined as the time from treatment initiation to emergence of mucosal lesion or death from any cause. Univariate and multivariate analysis were performed to evaluate the factors associated with those survival times; the factors included PS, extent of clinical target volume, treatment intent, N Stage (N1-2b vs N2c-N3), lymph node (LN) size, involved LN level (I-III vs IV-VI),

irradiated dose to the involved nodes and prophylactic/mucosal regions, surgical procedure, ECE status and chemotherapy.

Statistical analysis was performed using *JMP Pro version 11 (SAS Institute Inc., Cary, NC, USA)*. The log-rank test was used to compare differences between subgroups. The Chi-square test was used to investigate the relationship between variables. A p-value of 0.05 indicated significance.

Results

Patient characteristics and treatment details are summarized in Table 1 and 2. CT-based three dimensional RT was applied in 70.8% of all the patients. IMRT was not administered in this series.

The 5-year OS, PFS, NPFS and MPFS were 58.1%, 42.4%, 47.3% and 54.9%, respectively (Table 3, Figure 1,2). Recurrence after initial treatment occurred at 1-122 months (median 8 months) in 12 mucosal regions (9 in-field, 3 out-of-field), 29 nodal regions (22 in-field, 4 out-of-field and 3 both in- and out-of-field) and 31 distant metastases. Mucosal recurrences occurred most commonly in the oropharynx in 6 (4 in-field, 2 out-of-field); other mucosal regions included the hypopharynx in 2 (all in-field), hypopharynx / cervical esophagus in 1 (in-field),

oral floor in 1 (in-field), buccal mucosa in 1 (out-of-field) and larynx in 1 (in-field). Nodal recurrences occurred at 2-67 months (median 9 months) after initial treatment. The sites of distant metastases were as follows; lung (15), bone (13), liver (6), pleura (1) and skin (1).

Univariate analysis showed that lower N stage (N1-2b), non-bulky node (< 6 cm) and ECE negative were factors associated with favorable OS, PFS, NPFS and MPFS ($p<0.05$, Table 3). Radical surgery (modified radical neck dissection or selective neck dissection) also proved to be a factor for favorable OS, NPFS and MPFS. The median dose for palliative RT was significantly lower than for radical RT (median 34.0Gy, range 30.0-75.9Gy vs median 60.0Gy, range 12.6-86.8Gy) and the treatment outcome of palliative RT was significantly poor in OS, PFS and NPFS (Table 2,3). There was no statistical difference in other factors (extent of clinical target volume, involved LN level, irradiated dose to the involved nodes and prophylactic/mucosal regions and chemotherapy). Multivariate analysis, which was conducted for variables that proved to be prognostic factors by univariate analysis, showed that lower N stage and negative ECE status was the factor correlated with favorable OS, PFS, NPFS

and MPFS ($p<0.05$, Table 4). Radical treatment correlated with favorable OS and radical surgery was correlated with favorable MPFS.

As for acute adverse events, grade 3 mucositis was observed in 18 patients (combined with chemotherapy in 12) and grade 3 dermatitis in 8 (combined with chemotherapy in 7). As for severe late adverse events, grade 3 laryngeal edema was observed in 2 patients. Only one patient developed grade 4 brain infarction, possibly caused by the treatment.

Discussion

Radiotherapy, as well as surgery, is considered to be an important option to control NUP. The optimal method of radiotherapy for NUP had been controversial for a long time, as it is difficult to conduct randomized or prospective studies of this rare disease[30]. Some case studies have revealed therapeutic outcomes of NUP treated by radiotherapy combined with surgery and/or chemotherapy, which are summarized in Table 5[3,6,9,11,16-20]. Prognostic factors for survival are reported to be nodal stages, number of positive nodes, neck dissection, histopathological grading and ECE[3-5,7,9,18,19,21,22]. In this series, the 5-year OS rate was 58.1%, similar to the data in the previous studies. On

184 univariate analysis, favorable OS, PFS, NPFS and MPFS were associated with
185 lower N stage (N1-2b), non-bulky node (< 6 cm) and negative ECE status. On
186 multivariate analysis, lower N stage and ECE status was correlated with
187 improved survival. The results are also consistent with those of previous
188 reports[3-5,12,19,21]. The current National Comprehensive Cancer Network (NCCN)
189 guidelines for NUP (Version 1. 2017) provide recommendation for treatment with
190 neck dissection especially in N1 disease (category 2A). After neck dissection,
191 treatment strategies are determined by lymph node status. Definitive RT or
192 observation is recommended in N1 without ECE (category 2A). In the case of N2
193 or N3 without ECE, definitive RT or chemoradiation therapy is recommended
194 (category 2B). In the case of ECE, chemoradiation is recommended (category 1).
195 Definitive radiotherapy without surgery is recommended for N1 (category 2B)
196 and chemoradiation is recommended for N2 or N3 (category 2B). Induction
197 chemotherapy followed by systemic chemoradiation therapy is regarded as
198 category 3.
199 Unfortunately, there are some limitations in this series. The availability of
200 FDG-PET was low (31%) and the examination by NBI was not introduced. These
201 diagnostic procedures have been developed and enabled the detection of early

202 head and neck cancers. FDG-PET/CT has demonstrated relatively high
203 detection rates about 40% of NUP[23]. The usefulness of NBI with magnifying
204 endoscopy for detecting the primary site of NUP also has been reported.
205 Hayashi et al. investigated 46 patients of NUP and 26 lesions were suspected to
206 be cancerous lesions[24]. Of 26 patients, 16 lesions in 16 patients (35%, 16/46)
207 were identified to be squamous cell carcinoma. Another paradigm for the
208 diagnosis and management of NUP was reported using transitional robotic
209 surgery. Mehta et al. reported ten patients underwent transoral robotic base of
210 tongue resection[25]. All patients underwent a cervical biopsy, PET/CT, formal
211 endoscopy and bilateral tonsillectomy before this procedure but not identified
212 primary lesion. In nine of ten patients, pathologic examination revealed invasive
213 squamous cell carcinoma with a mean diameter of 0.9 cm.
214 Recently, TNM classification of Malignant Tumours 8th edition was published.
215 In this new classification, NUP was classified in three categories; EBV or
216 HPV/p16 negative or unknown, HPV/p16 positive and EBV positive. If EBV was
217 positive, it was staged as nasopharyngeal carcinomas and if p16 was positive, it
218 was staged as p16 positive oropharynx carcinomas. Treatment strategy for NUP
219 is considered to be subdivided by EBV or HPV/p16 status. Unfortunately, we

220 would not apply this new TNM classification in present analysis because EBV
221 and HPV/p16 status was not available in many cases. When we conducted this
222 study, EBV or HPV/p16 status was not routinely examined. In addition, TNM
223 classification is a bland-new classification, thus, we could not fully validate the
224 outcome to reported series.
225 One of the concerns of NUP treatment is the extent of the irradiation field. It has
226 been disputed as to whether contralateral neck and/or potential primary site
227 should be included or not. In our series, there were no significant differences in
228 OS, PFS, NPFS and MPFS in different irradiation fields. Reddy et al. reported
229 that subclinical metastases in the contralateral cervical lymph nodes were better
230 controlled by irradiation, including bilateral neck and pharyngeal mucosa than
231 ipsilateral neck irradiation (86% vs 56%, p=0.03)[10]. The occult primary emerged
232 in 8% after bilateral irradiation and in 44% after ipsilateral irradiation (p=0.0005).
233 This difference was anticipated to the fact that the mucosal region was contained
234 in irradiated fields in the bilateral group. Strojan et al. reported the comparison
235 between involved-field and extended-field in postoperative setting[26]. In
236 multivariate analysis, the only factor that influenced locoregional control was the
237 patients' age with older patients and the extent of RT field did not influence on

any outcome. In addition, acute and late toxicity was more common in patients with extended-field RT. They concluded Involved-field RT, although not superior over extended-field RT, seems to be a preferred treatment option due to significantly reduced toxicity and better prospects for successful salvage in case of contralateral neck recurrence or emergence of mucosal primary in the pharyngolaryngeal axis.

The rate of metachronous emergence of the primary site was 9.2% (12/130) in our series; the results were consistent with those of the previous reports[3,6,9,16,18,19]. Erkal et al. reported that 12 of 126 patients (10%) developed squamous cell carcinoma in the head and neck mucosa after initial treatment[9]. In the review of Nieder et al., the median rate of emergence of the primary site after extensive radiotherapy was 9.5% (range 2-13%), whereas it was 8.0% (range 5-44%) after ipsilateral radiotherapy[8]. As will be discussed later, IMRT with appropriate mucosal irradiation field settings is considered to lead to better treatment outcome by controlling the occult mucosal lesions.

In our series, the group that received (modified) radical neck dissection had better outcomes than the group without neck dissection in terms of OS, NPFS and MPFS on univariate analysis ($p<0.05$). Neck dissection followed by

256 postoperative radiotherapy is generally recognized as a standard approach, and
257 also has a clear advantage in evaluation for accurate disease extension and
258 histopathological features, such as ECE, thus providing additional information to
259 decide appropriate adjuvant therapeutic strategies such as combination with
260 chemotherapy. In our series, negative ECE status proved to be a favorable
261 prognostic factor in OS, PFS, NPFS and MPFS. Coster et al. reported clinical
262 results of 24 patients with NUP treated with curative resection by neck dissection
263 or excisional biopsy alone; ECE proved to be an unfavorable prognostic factor of
264 neck recurrence, cause-specific survival and overall survival[18]. They concluded
265 that patients with N1 disease without ECE could be managed by surgery alone,
266 while patients with N2 or higher nodal stage disease, and/or ECE would be
267 candidates for postoperative adjuvant radiation therapy.
268 Although IMRT was not administered in this series, it is considered to be a
269 promising procedure in treatment for NUP by offering appropriate target volume
270 coverage while sparing organs-at-risk compared with conventional
271 radiotherapy[11-13,15,20,27,28]. Villeneuve et al. reported promising results of NUP
272 using the IMRT technique[11]. They treated 25 patients with IMRT by a median
273 dose of 70 Gy with a radiation field including the bilateral neck and ipsilateral

pharyngeal mucosa; 17 underwent IMRT for definitive intent, 8 received it for postoperative setting, and 18 patients received platinum-based concurrent chemotherapy. With a median follow-up of 38 months, OS, disease-free survival and locoregional control rates were all 100% at 3 years with no emergence of primary cancer. Nine patients (36%) developed Grade 2 or greater xerostomia at 6 months, but only 2 (8%) of them developed the same grade of salivary toxicity after 24 months of follow-up. They concluded concurrent chemoradiotherapy with IMRT, including bilateral neck and ipsilateral putative pharyngeal mucosa, as the optimal therapeutic strategy. Janssen et al. reported individualized IMRT treatment approach to avoid extensive volumes while treating patients without oncological compromise[29]. Ipsilateral irradiation was preferred and treatment fields to the putative mucosal site or the contralateral neck were enlarged based on individual risk factors including clinical, surgical, histopathological and imaging information. The 3-year mucosal control rate, nodal control rate, and distant metastasis free survival were 100, 93, and 88%, respectively and there were no grade 2 or more late complications.

The role of adding systemic chemotherapy for improving local and distant control is another important issue. In our present series, the combination of

chemotherapy did not show advantages for improving OS, PFS, NPFS or MPFS. Argiris et al. reported a series of 25 patients who received concurrent chemoradiotherapy for N2 or N3 stage NUP[17]. Although this study was a retrospective analysis with a small sample size, they concluded that the addition of systemic chemotherapy may lead to improved locoregional and distant control, and long-term survival for good performance status patients with stage IV (N2 or N3) NUP. On the other hand, Chen et al. found no advantage of concurrent chemotherapy with regard to OS, PFS or locoregional control in a retrospective analysis of 60 patients treated by radiotherapy, of whom the majority (70%) underwent neck dissection[14].

The all concerns about NUP treatment strategy would be examined along with the new UICC/AJCC 8th TNM classification, EBV and HPV/p16 status should be required for accurate staging. Indeed, we do appreciate further investigation based on the 8th TNM classification should be desirable.

Conclusion

Our results suggest lower nodal stage, negative ECE status and combination of radical surgery showed a favorable impact on survival and disease control in

patients with NUP treated by radiotherapy. There were no significant differences in OS, PFS, NPFS and MPFS in different irradiation fields.

Acknowledgements

The part of this article was presented at the annual meeting of American Society for Therapeutic Radiation Oncology at 54th (Boston). I would like to thank Atsuro Terahara MD (Department of Radiology, Toho University Omori Medical Center, Tokyo, Japan), Masahiro Kenjo MD (Department of Radiation Oncology, Hiroshima University, Hiroshima, Japan), Takafumi Toshiyasu MD (Department of Radiation Oncology, Cancer Institute Hospital, Tokyo, Japan), Yu Okubo MD (Department of Radiation Oncology, Tokyo Women's Medical University School of Medicine, Tokyo, Japan), Sunao Tokumaru MD (Department of Heavy Particle Therapy and Radiation Oncology, Saga University, Japan) and Midori Kita MD (Department of Radiology, Tokyo Metropolitan Tama Medical Center, Tokyo, Japan), for taking care of by the registration of cases. I would also like to show my greatest appreciation to Prof. Masataka Uetani who provided helpful comments and suggestions.

Conflict of interest statement

None declared.

References

1. Waltonen JD, Ozer E, Hall NC, et al Metastatic carcinoma of the neck of unknown primary origin: evolution and efficacy of the modern workup. Arch Otolaryngol Head Neck Surg 2009; 135:1024-9,

2. Miller FR, Karnad AB, Eng T, et al: Management of the unknown primary carcinoma: long-term follow-up on a negative PET scan and negative panendoscopy. Head Neck 2008;30:28-34

3. Grau C, Johansen LV, Jakobsen J, et al: Cervical lymph node metastases from unknown primary tumours. Results from a national survey by the Danish Society for Head and Neck Oncology. Radiother Oncol 2000;55:121-9

4. Eldeeb H, Hamed RH: Squamous cell carcinoma metastatic to cervical lymph nodes from unknown primary origin: the impact of chemoradiotherapy. Chin J Cancer 2012;31:484-90

5. Wallace A, Richards GM, Harari PM, et al: Head and neck squamous cell carcinoma from an unknown primary site. Am J Otolaryngol 2011;32:286-90

6. Ligey A, Gentil J, Crehange G, et al: Impact of target volumes and radiation technique on loco-regional control and survival for patients with unilateral cervical lymph node metastases from an unknown primary. Radiother Oncol 2009;93:483-7

7. Beldi D, Jereczek-Fossa BA, D'Onofrio A, et al: Role of radiotherapy in the treatment of cervical lymph node metastases from an unknown primary site: retrospective analysis of 113 patients. Int J Radiat Oncol Biol Phys 2007;69:1051-8

8. Nieder C, Ang KK: Cervical lymph node metastases from occult squamous cell carcinoma. Curr Treat Options Oncol 2002;3:33-40

9. Erkal HS, Mendenhall WM, Amdur RJ, et al: Squamous cell carcinomas metastatic to cervical lymph nodes from an unknown head-and-neck mucosal site treated with radiation therapy alone or in combination with neck dissection. Int J Radiat Oncol Biol Phys 2001;50:55-63

10. Reddy SP, Marks JE: Metastatic carcinoma in the cervical lymph nodes from an unknown primary site: results of bilateral neck plus mucosal irradiation vs. ipsilateral neck irradiation. Int J Radiat Oncol Biol Phys 1997;37:797-802

11. Villeneuve H, Despres P, Fortin B, et al: Cervical lymph node metastases from unknown primary cancer: a single-institution experience with intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2012;82:1866-71
12. Shoushtari A, Saylor D, Kerr KL, et al: Outcomes of patients with head-and-neck cancer of unknown primary origin treated with intensity-modulated radiotherapy. Int J Radiat Oncol Biol Phys 2011;81:e83-91
13. Sher DJ, Balboni TA, Haddad RI, et al: Efficacy and toxicity of chemoradiotherapy using intensity-modulated radiotherapy for unknown primary of head and neck. Int J Radiat Oncol Biol Phys 2011;80:1405-11
14. Chen AM, Farwell DG, Lau DH, et al: Radiation therapy in the management of head-and-neck cancer of unknown primary origin: how does the addition of concurrent chemotherapy affect the therapeutic ratio? Int J Radiat Oncol Biol Phys 2011;81:346-52
15. Frank SJ, Rosenthal DI, Petsuksiri J, et al: Intensity-modulated radiotherapy for cervical node squamous cell carcinoma metastases from unknown head-and-neck primary site: M. D. Anderson Cancer Center outcomes and patterns of failure. Int J Radiat Oncol Biol Phys 2010; 78:1005-10
16. Shehadeh NJ, Ensley JF, Kucuk O, et al: Benefit of postoperative chemoradiotherapy for patients with unknown primary squamous cell carcinoma of the head and neck. Head Neck 2006;28:1090-8
17. Argiris A, Smith SM, Stenson K, et al: Concurrent chemoradiotherapy for N2 or N3 squamous cell carcinoma of the head and neck from an occult primary. Ann Oncol 2003;14:1306-11
18. Coster JR, Foote RL, Olsen KD, et al: Cervical nodal metastasis of squamous cell carcinoma of unknown origin: indications for withholding radiation therapy. Int J Radiat Oncol Biol Phys 1992;23:743-9
19. Aslani M, Sultanem K, Voung T, et al: Metastatic carcinoma to the cervical nodes from an unknown head and neck primary site: Is there a need for neck dissection? Head Neck 2007;29:585-90
20. Klem ML, Mechalakos JG, Wolden SL, et al: Intensity-modulated radiotherapy for head and neck cancer of unknown primary: toxicity and preliminary efficacy. Int J Radiat Oncol Biol Phys 2008;70:1100-7
21. Colletier PJ, Garden AS, Morrison WH, et al: Postoperative radiation for squamous cell carcinoma metastatic to cervical lymph nodes from an unknown primary site: outcomes and patterns of failure. Head Neck 1998;20:674-81
22. Patel RS, Clark J, Wyten R, et al: Squamous cell carcinoma from an unknown head and neck primary site: a "selective treatment" approach. Arch Otolaryngol Head Neck Surg 2007; 133:1282-7

394 23. Kwee TC, Kwee RM: Combined FDG-PET/CT for the detection of unknown primary tumors:
395 systematic review and meta-analysis. Eur Radiol 2009;19:731-44
396 24. Hayashi T, Muto M, Hayashi R, et al: Usefulness of narrow-band imaging for detecting the
397 primary tumor site in patients with primary unknown cervical lymph node metastasis. Jpn J Clin
398 Oncol 2010;40:537-41
399 25. Mehta V, Johnson P, Tassler A, et al: A new paradigm for the diagnosis and management of
400 unknown primary tumors of the head and neck: a role for transoral robotic surgery. Laryngoscope
401 2013;123:146-51
402 26. Strojan P, Kokalj M, Zadnik V, et al: Squamous cell carcinoma of unknown primary tumor
403 metastatic to neck nodes: role of elective irradiation. Eur Arch Otorhinolaryngol 2016;
404 273:4561-4569
405 27. Madani I, Vakaet L, Bonte K, et al: Intensity-modulated radiotherapy for cervical lymph node
406 metastases from unknown primary cancer. Int J Radiat Oncol Biol Phys 2008;71:1158-66,
407 28. Lu H, Yao M, Tan H: Unknown primary head and neck cancer treated with
408 intensity-modulated radiation therapy: to what extent the volume should be irradiated. Oral Oncol
409 2009;45:474-9,
410 29. Janssen S, Glanzmann C, Huber G, et al: Individualized IMRT treatment approach for
411 cervical lymph node metastases of unknown primary. Strahlenther Onkol 2014;190:386-93,
412 30. Radiation Therapy in Treating Patients With Metastases to the Lymph Nodes in the Neck
413 From an Unknown Primary Tumor. URL: https://clinicaltrials.gov/ct2/show/study/NCT 00047125

Table 1. Patient Characteristics

Characteristic	Value	
Age at diagnosis (median)	65	(39-87)
Gender		
Male	119	(92%)
Female	11	(8%)
Histology		
Squamous cell carcinoma	122	(94%)
Undifferentiated carcinoma	8	(6%)
Nodal Stage		
N1	10	(8%)
N2a	26	(20%)
N2b	43	(33%)
N2c	12	(9%)
N3	39	(30%)
Diagnostic Evaluation		
CT	128	(98%)
MR	82	(63%)
FDG-PET	40	(31%)
Laryngoscopy	96	(74%)
Tonsillectomy	1	(1%)
Involved N level		
I	14	(11%)
II	98	(75%)
III	39	(30%)
IV	43	(33%)
V	14	(11%)
VI	3	(2%)

Abbreviations: CT, Computed Tomography MR, Magnetic Resonance; FDG-PET, 18-Fluoro-deoxyglucose Positron Emission Tomography

Table 2. Treatment Details

Treatment Intent		
Radical	17	(13%)
Palliative	113	(87%)
Surgical Treatment		
FNA Only	49	(38%)
Excisional Biopsy	17	(13%)
Selective Neck Dissection	11	(8%)
Modified Radical Neck Dissection	53	(41%)
Chemotherapy		
Yes	66	(51%)
No	64	(49%)
Neck Dissection + Chemotherapy	27	(21%)
Involved Nodal Dose		
Median	60.0 Gy (12.6 – 86.8 Gy)	
Prophylactic Nodal Dose		
Median	50.4 Gy (12.6 - 72.0 Gy)	
Mucosal Dose		
Median	50.4 Gy (12.6 – 71.0 Gy)	
RT Volume		
Local Only	11	(8%)
Local + Mucosa	2	(2%)
Ipsilateral Neck	31	(24%)
Ipsilateral Neck + Mucosa	7	(5%)
Bilateral Neck	3	(2%)
Bilateral Neck + Mucosa	76	(58%)
Mucosal Volume / Irradiated Dose (median dose)		
Nasopharynx	70	(54%) / 12.6-70.0Gy (50.0Gy)
Oropharynx / Oral Cavity	76	(58%) / 12.6-71.0Gy (50.0Gy)
Hypopharynx / Larynx	81	(62%) / 12.6-70.0Gy (50.0Gy)
Cervical Esophagus	51	(39%) / 12.6-70.0Gy (46.0Gy)

Abbreviations: FNA, Fine Needle Aspiration; RT, Radiotherapy

Table 3. Univariate analysis for overall survival, progression free survival, neck progression free survival and mucosal progression free survival

Factor	No. of patient	OS		PFS		NPFS		MPFS	
		%	P-Value	%	P-Value	%	P-Value	%	P-Value
Overall	130	58.1		42.4		47.3		54.9	
Treatment Intent									
Radical	113	60.3		44.2		49.1		56.3	
Palliative	17	30.7	<0.05	29.6	<0.05	34.8	<0.05	41.2	0.17
PS									
0-1	107	61.8		46.7		52.7		60.0	
2-3	13	40.0	0.13	40.0	0.91	40.0	0.57	44.4	0.48
N-Stage									
1-2b	79	69.2		51.1		57.3		70.7	
2c-3	51	37.1	<0.01	27.5	<0.01	31.8	<0.01	33.1	<0.01
N-Size									
< 6 cm	91	66.6		49.7		56.6		61.6	
≥ 6 cm	39	34.9	<0.01	26.6	<0.05	31.2	<0.01	36.9	<0.01
ECE									
Positive	34	75.5		37.0		41.1		45.5	
Negative	44	53.4	<0.01	56.4	<0.01	62.9	<0.01	71.1	<0.01
Dose to Involved Nodes (Radical Intent)									
< 50 Gy	8	72.9		60.0		60.0		72.9	
≥ 50 Gy	105	59.3	0.78	43.1	0.93	48.4	0.80	55.0	0.56
Dose to Prophylactic Nodes (Radical Intent)									
< 50 Gy	46	55.7		34.2		41.8		55.8	
≥ 50 Gy	67	63.3	0.59	50.9	0.08	54.1	0.14	56.7	0.84
Radical Surgery									
Yes	64	67.2		49.0		43.2		63.9	
No	66	48.5	<0.05	35.6	0.07	38.4	<0.05	45.3	<0.05
Chemotherapy									
Yes	67	54.7		41.1		46.8		53.9	
No	63	61.4	0.44	43.6	0.63	47.0	0.78	55.4	0.57
RT Field									
Neck only	46	44.7		31.1		33.8		45.5	
Neck + mucosa	84	65.5	0.24	48.5	0.24	54.8	0.08	59.7	0.46
Involved Level									
I-III	46	57.6		42.0		47.4		52.3	
IV-VI	84	60.1	0.91	44.1	0.76	49.4	0.90	60.1	0.56

Abbreviations: OS, Overall Survival; PFS, Progression Free Survival; NPFS, Neck Progression Free Survival; MPFS, Mucosal Progression Free Survival
PS, Performance Status; RT, Radiotherapy; ECE, Extracapsular Extension

Table 4. Multivariate analysis for overall survival, progression free survival, neck progression free survival and mucosal progression free survival

Factor	Valuable type	OS			PFS			NPFS			MPFS		
		HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value	HR	95% CI	P-value
Treatment Intent	Radical vs Palliative	0.34	0.13-1.00	<0.05	0.44	0.19-1.08	0.07	0.44	0/19-1.08	0.07	0.45	0.17-1.43	0.16
N stage	N1-2b vs N2c-3	0.37	0.20-0.69	<0.01	0.48	0.29-0.80	<0.01	0.48	0.29-0.80	<0.01	0.40	0.22-0.72	<0.01
Radical surgery	Yes vs No	0.44	0.19-1.12	0.08	0.71	0.36-1.50	0.35	0.71	0.36-1.520	0.36	0.39	0.18-0.89	<0.05
Extracapsular Extension	Negative vs Positive	0.30	0.12-0.66	<0.01	0.46	0.25-0.87	0.02	0.46	0.25-0.87	0.02	0.32	0.15-0.67	<0.01

Abbreviations: OS, Overall Survival; PFS, Progression Free Survival; NPFS, Neck Progression Free Survival; MPFS, Mucosal Progression Free Survival; HR; Hazard Ratio

Table 5. Selected series of cervical patients with squamous cell carcinoma of unknown primary

Author	Year	No. of patients	Treatment Method (N)	5Y OS (%)	Metachronous primaries (%)
Coster	1992	24	S (24)	66	4
Grau	2000	273	S (23), R (224), S+R (26)	36	12
Erkal	2001	126	S+R (70), R (56)	47	10
Arigiris	2003	25	S+R+C (22), R+C (3)	75	0
Shehadeh	2006	37	S+R+C (37)	NC	3
Aslani	2007	61	R (41), S+R (20)	79	7
Klem	2008	21	R (IMRT) (+S), (+C)	85 (2Y)	0
Ligey	2009	95	R (+S 79), (+C 43)	24	9
Villeneuve	2012	25	R (IMRT) (+S 8), (+C 18)	100 (3Y)	0
Janssen	2014	28	R (IMRT) (+S 20), (+C 20)	76 (3Y)	0
Strojan	2016	126	R (+S 126), (+C 19)	57	9
Present	2017	130	R (26), (+S 38), (+C 40), (+S+C 26)	58	9

Abbreviations: OS, Overall Survival; S, Surgery; R, Radiotherapy; C, Chemotherapy; IMRT, Intensity Modulated Radiotherapy; NC, Not Calculated

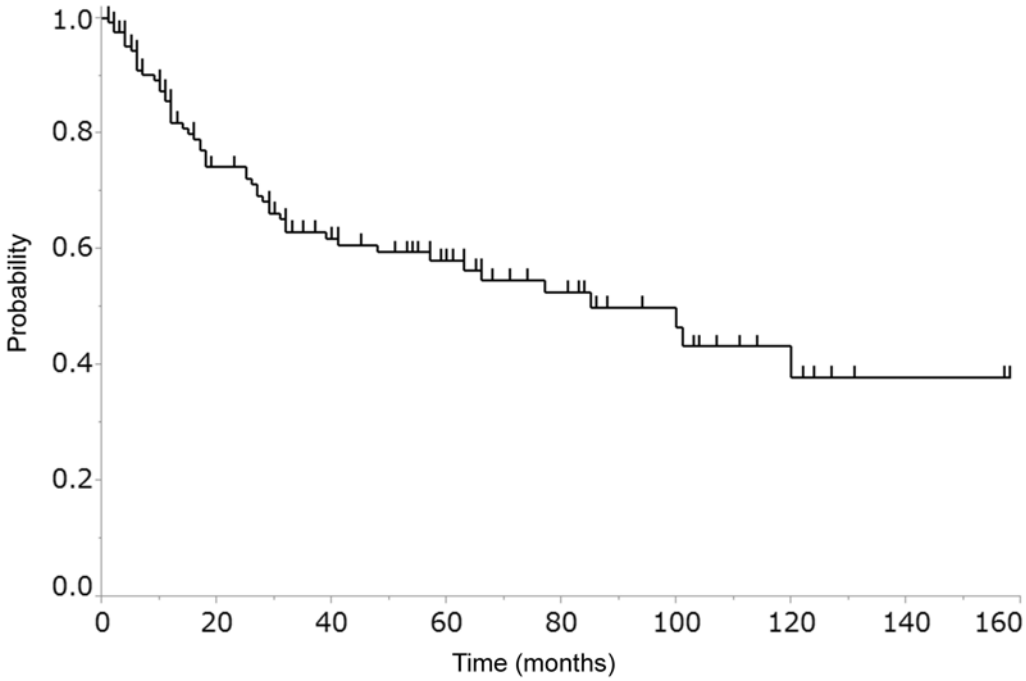

Fig.1 Overall Survival

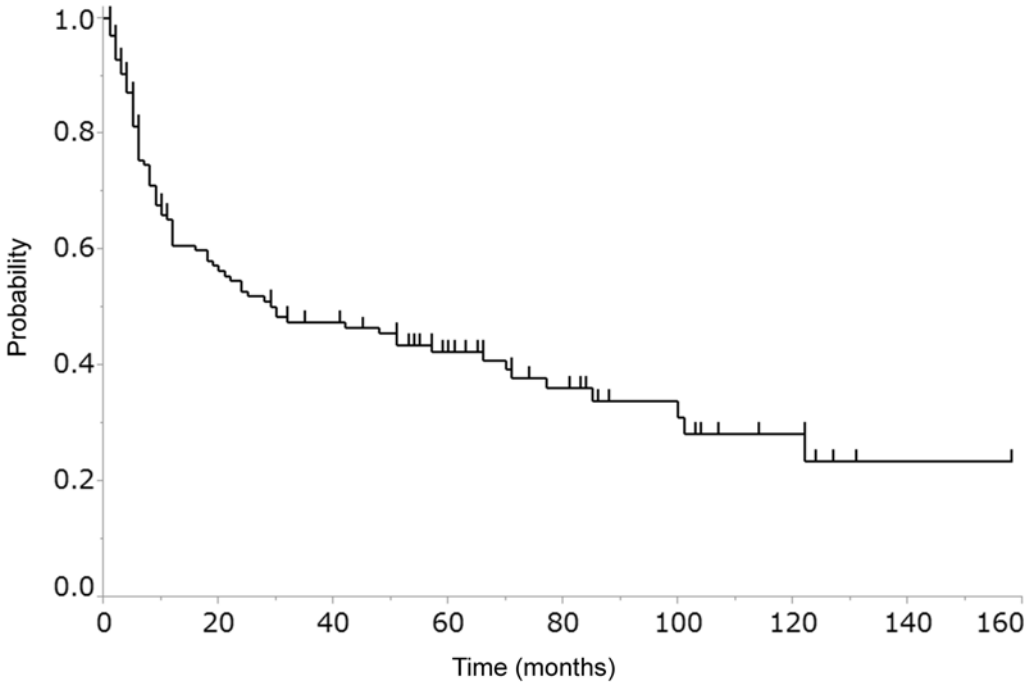

Fig.2 Progression Free Survival