厚生労働科学研究委託費
革新的がん医療実用化研究事業

頭頸部表在がんに対する診断・治療法の確立に関する研究
- 頭頸部表在癌全国登録調査 -

平成26年度　委託業務成果報告書

業務主任者　　林　隆一

平成27（2015）年3月

本報告書は、厚生労働省の厚生労働科学研究委託事業（革新的がん医療実用化研究事業）による委託業務として、独立行政法人国立がん研究センターが実施した平成26年度「頭頸部表在がんに対する診断・治療法の確立に関する研究 - 頭頸部表在癌全国登録調査 - 」の成果を取りまとめたものです。

厚生労働科学研究委託費
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平成27（2015）年3月

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Ⅰ．研究組織

区分	氏名	所属	職名
研究代表者	林　隆一	（独）国立がん研究センター東病院　頭頸部外科	科長
研究分担者	岡本　牧人	北里大学医学部　耳鼻咽喉科	教授
	武藤 学	京都大学医学部附属病院　がん薬物治療科	教授
	門馬　久美子	都立駒込病院　内視鏡科	部長
	大森　泰	川崎市立井田病院　内視鏡治療部	部長
	渡邉　昭仁	恵佑会札幌病院　耳鼻咽喉科	主任部長
	川端　一嘉	がん研究会有明病院　頭頸科	部長
	藤井　誠志	（独）国立がん研究センター東病院　臨床開発センター	ユニット長

II. 委託業務成果報告

厚生労働科学研究委託費（革新的がん医療実用化研究事業）
委託業務成果報告（総括）

頭頸部表在がんに対する診断・治療法の確立に関する研究
- 頭頸部表在がん全国登録調査 -

業務主任者又　　林 隆一　国立がん研究センター東病院

研究要旨
頭頸部表在がんに対する標準的な診断・治療法は確立していない。本研究の目的は経口的に切除された頭頸部表在がんを解析することで臨床病理学的特徴を解明し、頭頸部癌取扱い規約に反映する。また、経口腔的切除の安全性と有効性を確認し内視鏡的治療の保険承認申請を行うことである。頭頸部表在がんはNBIや拡大内視鏡など内視鏡の技術進歩と、食道領域における頭頸部がんのハイリスク因子の抽出より発見された新しい疾患概念であり病態は解明されていない。また国際的にもその取り扱いについては標準化されていないため、登録体制の確立と多施設での症例集積と解析が必要である。2009 年 12 月までに経口腔的切除が行われた頭頸部表在がん症例の臨床情報の Web 登録体制を構築、北里大学医学部附属臨床研究センターにデータセンターを設置し登録の体制を整えた。平成 25 年 11 月末までに 27 施設 599 症例が登録された。平成 26 年 10 月までに 11 施設 161 例の症例登録が確定した。また平成 26 年 12 月までに中央病理診断が終了した。中央病理診断においては今後の解析結果の公表を踏まえて、海外との整合性も考慮し各病理医間で診断の統一を図っている。早期発見・早期治療につながる研究であり、頭頸部がんの治療成績の向上に寄与するものである。また、頭頸部領域の発がんメカニズムの解明や二次発がん予防の研究に貢献しうる。

研究分担者

岡本　牧人	北里大学医学部 耳鼻咽喉科
武藤　学	京都大学大学院医学研究科
門馬　久美子	都立駒込病院 内視鏡科
大森　泰	川崎市立井田病院内視鏡治療部
渡邊　昭仁	恵佑会札幌病院 耳鼻咽喉科
川端　一嘉	がん研究会有明病院 頭頸科
藤井　誠志	国立がん研究センター東病院 臨床開発センター

A. 研究目的

頭頸部表在がんは狭帯領域内視鏡（NBI 内視鏡）をはじめとする内視鏡光学技術の向上と頭頸部がん合併の危険因子の解明によって発見されるに至った新しい疾患概念である。このような希少がんに対して登録体制を構築し、経口的に切除された頭頸部表在がんを解析することで、臨床病理学的特徴を解明し、頭頸部癌取扱い規約に反映する。また、経口腔的切除の安全性と有効性を確認し内視鏡的治療の保険承認申請を行うことが本研究の目的である。

B. 研究方法

登録対象

2009 年12 月までに経口腔的切除がおこなわれている頭頸部表在がん症例で組織学的に頭扁平上皮がんと診断されているものを対象として集積した。

Web 登録とデータベース管理

病院記録とその他の関連記録を使用して登録項目を登録する。登録は Web 上の登録ファイルを用いて行う。登録された登録項目はすでに構築されているデータベースに記録される。各登録施設より各施設における個人情報管理責任者を研究事務局に申請し個人情報管理をおこなう。データベースの管理は研究事務局が行う。データセンターは北里大学医学部附属臨床研究センターに設置した。

内視鏡画像登録

内視鏡画像所見と病理組織学的所見の対比をおこなうために、本研究では全登録例の内視鏡画像のWeb登録を行うこととした。

中央病理診断

全登録例の生検標本と切除標本を対象として、中央病理診断基準作成委員会でまとめた診断基準を用いて中央病理診断判定委員が標本の病理診断を行い、解析には中央病理診断の結果を採用した。各登録施設の登録代表者は中央病理診断開催前に該当する標本を各施設で匿名化して中央病理診断事務局に送付する。

（倫理面への配慮）

本研究に関係する全ての研究者は「ヘルシンキ宣言」や「疫学研究に関する倫理指針」に従って本登録を実施し、被験者の人権保護に努める。本研究は「診断・治療等の医療行為について、

当該方法の有効性・安全性を評価するため、診療録等の診療情報を収集・集計しておこなう観察研究」であることから、「疫学研究の倫理指針」となる。また、本研究は試料の採取を目的としていないので、「研究者等は、当該研究の目的を含む研究の実施についての情報を公開する」ことで対応することとする。個人情報の保護に関しては、各登録施設は症例個人を特定しえる氏名、患者ID番号は登録せず、施設符号化番号を与え匿名化したうえで、その他の登録項目についてWeb上の登録ファイルに登録し、研究事務局が管理するデータベースに記録する。各登録施設の患者ID番号と施設符号化番号の対応表は、各登録施設における個人情報管理者が「医療情報システムの安全管理に関するガイドライン第4版」に基づき、組織的安全対策、物理的安全対策、技術的安全対策、人的安全対策を行い、その管理を徹底する。本研究の参加に際しては、本研究実施計画書が各施設の倫理審査委員会もしくは機関審査委員会で承認されなければならない。

C. 研究結果

平成25年11月末までに27施設599症例が登録された。平成26年10月までに11施設161例の症例登録が確定した。また平成26年12月までに中央病理診断が終了した。平成26年6月より中央内視鏡診断を開始した。内視鏡画像は撮影条件に差があることから評価可能な写真を抽出するためにスクリーニングを実施した。のべ800症例の内視鏡画像を2名で1次スクリーニングを実施し27施設中26施設において終了した。実施した会議は以下の通りである。

中央病理診断委員会

2014/6/14　第5回中央病理診断 慶応大学病院
2014/11/9　第6回中央病理診断 秋田大学病院

臨床病理学的検討会

2014/5/11　第7回臨床病理学的検討判定会 国立がん研究センター東病院
2014/6/1　第8回臨床病理学的検討判定会 国立がん研究センター東病院
2014/7/5　第9回臨床病理学的検討判定会 国立がん研究センター東病院
2014/8/10　第10回臨床病理学的検討判定会 国立がん研究センター東病院
2014/9/14　第11回臨床病理学的検討判定会 国立がん研究センター東病院
2014/11/9　第12回臨床病理学的検討判定会 秋田大学病院
2014/11/30　第13回臨床病理学的検討判定会 国立がん研究センター東病院
2014/12/23　第14回臨床病理学的検討判定会 国立がん研究センター東病院
2014/12/29　第15回臨床病理学的検討判定会 国立がん研究センター東病院

中央内視鏡判定委員会

2014/6/13　第1回中央内視鏡診断 国立がん研究センター東病院
2015/2/13　第2回中央内視鏡診断全体班会議 ステーションコンファレンス東京

班会議

2014/11/2　第1回班会議 フクラシア東京ステーション

D. 考察

頭頸部表在がんに対する標準的な診断・治療法は確立していない。国際的にも認知されておらず、病態も明らかでないために本研究を通じて臨床病理学的特徴を解明し、診断・治療などその取り扱いを標準化することは意義があるといえる。中央病理診断においては今後の解析結果の公表を踏まえて、海外との整合性も考慮し各病理医間で診断の統一を図っている。早期発見・早期治療につながる研究であり、頭頸部がんの治療成績の向上に寄与すると同時に、頭頸部領域の発がんメカニズムの解明や二次発がん予防の研究に貢献しうる。

E. 結論

頭頸部表在がんの病態解析、診断・治療の標準かを目的として、臨床情報のWeb登録体制を構築し、北里大学医学部附属臨床研究センターにデータセンターを設置、平成25年11月末までに27施設599症例が登録、平成26年10月までに11施設161例の症例登録が確定し、平成26年12月までに中央病理診断が終了した。

F. 健康危険情報

該当なし

G. 研究発表

1. 論文発表

1. Ichiro Tateya, Shuko Morita, Manabu Muto, Shinichi Miyamoto, Tomomasa Hayashi, Makiko Funakoshi, Ikuo Aoyama, Shigeru Hirano, Morimasa Kitamura, Seiji Ishikawa, Yo Kishimoto, Mami Morita, Patnarin Mahattanasakul, Satoshi Morita, Juishi Ito. Magnifying endoscope with NBI topredict the depth of invasion in laryngo-pharyngeal cancer. Laryngoscope. 2014 Nov 24.

2. Satake H, Yano T, Muto M, Minashi K, Yoda Y, Kojima T, Oono Y, Ikematsu H, Aoyama I, Morita S, Miyamoto S, Fujii S, Yoshizawa A, Ochiai A, Hayashi R, Kaneko K. Clinical outcome after endoscopic resection for superficial pharyngeal squamous cell carcinoma invading the subepithelial layer. Endoscopy. 2014 Sep 30. [Epub ahead of print]

3. Yagishita A, Fujii S, Yano T, Kaneko K. Endoscopic findings using narrow-band imaging to distinguish between basal cell

hyperplasia and carcinoma of the pharynx. Cancer Sci. 2014;105:857-61.

4. 渡邉昭仁. 下咽頭早期癌に対して経口手術がどこまで可能かわからない。JHONS 30(9): 1345-1347, 2014.

2.学会発表

1. 当院における頭頸部表在癌の治療成績（ポスター）. 森田 周子、武藤 学、楯谷 一郎、横山 顕礼、青山 育雄、堀松 高博、江副 康正、宮本 心一、千葉 勉. 第68回日本食道学会学術集会第68回日本食道学会学術集会. 2014/7/4 東京

2. 頭頸部表在癌におけるNBI診断のコツを教えます-消化器科と耳鼻科の視点から-（学術セミナー）（口頭）. 武藤 学、渡邉 昭仁. 第38回日本頭頸部癌学会. 2014/6/13 東京

3. 当院におけるELPS導入後の課題(口頭). 岡本旅人、堅田親利、岡本牧人. 第15回頭頸部表在癌研究会. 2014/6/14 東京

4. 当科における頭頸部表在癌の診断と治療(口頭). 岡本旅人、中山明仁、宮本俊輔、清野由輩、加納孝一、細野浩史、堅田親利、岡本牧人. 第28回北里腫瘍フォーラム. 2015/1/30

5. Integrated Robotic Surgical Approach for Oropharyngeal Cancer. Kawabata K, SEVERANCE ROBOTIC SURGERY symposium. 2014 KOREA

6. 喉頭癌に対するCO2レーザー切除後の音声機能. 渡邉昭仁、谷口雅信、木村有貴. 第35回東日本音声外科研究会. 2014/4/19 東京

7. 耳鼻科用電子スコープ内視鏡所見と上部消化管内視鏡所見の比較検討. 渡邉昭仁、谷口雅信. 第115回日本耳鼻咽喉科学会. 2014/5/1 福岡

8. 下咽頭表在癌. 渡邉昭仁. 第5回頭頸部癌教育セミナー. 2014/6/11 東京

9. 頭頸部表在癌におけるNBI診断のコツ教えます～消化器と耳鼻科の視点から～. 渡邊昭仁. 第38回頭頸部外科学会. 2014/6/13 東京

10. ELPSの適応と限界. 渡邊昭仁. 第27回日本口腔咽頭科学会. 2014/9/12 札幌

11. 耳鼻咽喉科NBI内視鏡での表在癌診断. 渡邊昭仁. GI net club. 2014/9/27 大阪

12. 頭頸部癌に対する経口手術療法. 渡邊昭仁. 札幌耳鼻咽喉科疾患を考える会. 2014/10/25 札幌

13. 上部消化管内視鏡補助下彎曲喉頭鏡展開で行う声門上癌に対する経口手術. 渡邊昭仁、谷口雅信、木村有貴. 第16回耳鼻咽喉科手術支援システム・ナビ研究会. 2014/11/8 米子

14. 頸部食道癌下咽頭伸展例に対するELPSを応用した喉頭温存手術. 渡邊昭仁、谷口雅信、木村有貴、細川正夫. 第66回日本気管食道科学会. 2014/11/13 高知

15. 彎曲喉頭鏡を用いた中咽頭側壁癌経口切除術. 渡邊昭仁、谷口雅信、木村有貴. 第25回日本頭頸部外科学会総会. 2015/1/29 大阪

16. Endoscopic Laryngo-Pharyngeal Surgery for superficial pharyngeal cancers. Watanabe A, TaniguchiM., Kimura Y. 1st International minimally invasive surgery conference. 2015/3/19-20 Hong Kong

H. 知的財産権の出願・登録状況
（予定を含む）

1.特許取得
該当なし

2. 実用新案登録
該当なし

3. その他
該当なし

III. 学会等発表実績

学 会 等 発 表 実 績

委託業務題目「頭頸部表在がんに対する診断・治療法の確立に関する研究
- 頭頸部表在癌全国登録調査 - 」

施設名　国立がん研究センター

1．学会等における口頭・ポスター発表

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
当院における頭頸部表在癌の治療成績（ポスター）	森田　周子 武藤　学 楯谷　一郎 横山　顕礼 青山　育雄 堀松　高博 江副　康正 宮本　心一 千葉　勉	第68回日本食道学会学術集会	2014年7月4日	国内
頭頸部表在癌におけるNBI診断のコツを教えます-消化器科と耳鼻科の視点から-学術セミナー（口頭）	武藤 学 渡邉　昭仁	第38回日本頭頸部癌学会	2014年6月13日	国内
当院におけるELPS導入後の課題（口頭）	岡本旅人 堅田親利 岡本牧人	第15回頭頸部表在癌研究会	平成26年6月14日	国内
当科における頭頸部表在癌の診断と治療（口頭）	岡本旅人 中山明仁 宮本俊輔 清野由輩 加納孝一 細野浩史 堅田親利 岡本牧人	第28回北里腫瘍フォーラム	平成27年1月30日	国内
Integrated Robotic Surgical Approach for Oropharyngeal Cancer	川端　一嘉	ソウル大学 3rdINTERNATIONAL SEVERANCE ROBOTIC SUGERY	2014年	韓国
喉頭癌に対するCO2レーザー切除後の音声機能	渡邉昭仁 谷口雅信 木村有貴	第35回東日本音声外科研究会	平成26年4月19日	国内（東京）
耳鼻科用電子スコープ内視鏡所見と上部消化管内視鏡所見の比較検討	渡邉昭仁 谷口雅信	第115回日本耳鼻咽喉科学会	平成26年5月15日	国内（福岡）
下咽頭表在癌	渡邉昭仁	第5回頭頸部癌教育セミ	平成26年6月11日	国内（東京）
頭頸部表在癌におけるNBI診断のコツ教えます～消化器と耳鼻科の視点から～	渡邉昭仁	第38回頭頸部外科学会	平成26年6月13日	国内（東京）
ELPSの適応と限界	渡邉昭仁	第27回日本口腔咽頭科学会	平成26年9月12日	国内（札幌）
耳鼻咽喉科NBI内視鏡での表在癌診断	渡邉昭仁	GI net club	平成26年9月27日	国内（大阪）
頭頸部癌に対する経口手術療法	渡邉昭仁	札幌耳鼻咽喉科疾患を考える会	平成26年10月25日	国内（札幌）
上部消化管内視鏡補助下彎曲喉頭鏡展開で行う声門上癌に対する経口手術	渡邉昭仁 谷口雅信 木村有貴	第16回耳鼻咽喉科手術支援システム・ナビ研究会	平成26年11月8日	国内（米子）
頸部食道癌下咽頭伸展例に対するELPSを応用した喉頭温存手術	渡邉昭仁 谷口雅信 木村有貴 細川正夫	第66回日本気管食道科学会	平成26年11月13日	国内（高知）

発表した成果（発表題目、口頭・ポスター発表の別）	発表者氏名	発表した場所（学会等名）	発表した時期	国内・外の別
彎曲喉頭鏡を用いた中咽頭側壁癌経口切除術	渡邉昭仁 谷口雅信 木村有貴	第25回日本頭頸部外科学会総会	平成27年1月29日	国内（大阪）
Endoscopic Laryngo-Pharyngeal Surgery for superficial pharyngeal cancers	Watanabe A, TaniguchiM. Kimura Y.	1st International minimally invasive surgery conference	平成27年3月19-20日	国外（Hong Kong）

２．学会誌・雑誌等における論文掲載

掲載した論文（発表題目）	発表者氏名	発表した場所（学会誌・雑誌等	発表した時期	国内・外の別
Endoscopic disgnosis for superficial neoplasia at the head and neck regions.	Manabu Muto.	Eur J Cancer Prev.	in press	国外
Magnifying endoscope with NBI topredict the depth of invasion in laryngo-pharyngeal cancer.	Ichiro Tateya Shuko Morita Manabu Muto Shinichi Miyamoto Tomomasa Hayashi Makiko Funakoshi Ikuo Aoyama Shigeru Hirano Morimasa Kitamura Seiji Ishikawa Yo Kishimoto Mami Morita Patnarin Mahattanasakul Satoshi Morita	Laryngoscope.	2014 Nov 24	国外
Clinical outcome after endoscopic resection for superficial pharyngeal squamous cell carcinoma invading the subepithelial layer.	Satake H Yano T Muto M Minashi K Yoda Y Kojima T Oono Y Ikematsu H Aoyama I Morita S Miyamoto S Fujii S Yoshizawa A Ochiai A Hayashi R Kaneko K	Endoscopy.	2014 Sep 30. [Epub ahead of print]	国外
Endoscopic findings using narrow-band imaging to distinguish between basal cell hyperplasia and	Yagishita A Fujii S Yano T Kaneko K	Cancer Sci. 2014;105:857-61.	2014	国外
下咽頭早期癌に対して経口手術がどこまで可能かわからない。	渡邉昭仁	JHONS 30(9): 1345-1347, 2014.	2014	国内

IV. 研究成果の刊行物・別刷

The Laryngoscope

Magnifying Endoscope With NBI to Predict the Depth of Invasion in Laryngo-Pharyngeal Cancer

Ichiro Tateya, MD, PhD; Shuko Morita, MD; Manabu Muto, MD, PhD; Shin'ichi Miyamoto, MD, PhD; Tomomasa Hayashi, MD, PhD; Makiko Funakoshi, MD; Ikuo Aoyama, MD; Shigeru Hirano, MD, PhD; Morimasa Kitamura, MD, PhD; Seiji Ishikawa, MD, PhD; Yo Kishimoto, MD, PhD; Mami Morita, MD; Patnarin Mahattanasakul, MD; Satoshi Morita, PhD; Juichi Ito, MD, PhD

Objectives/Hypothesis: To examine if macroscopic classification with a magnifying gastrointestinal endoscope with narrow band imaging (ME-NBI) is useful in predicting pathological depth of tumor invasion in laryngo-pharyngeal cancer.

Study Design: Retrospective study.

Methods: Preoperative endoscopy reports and postoperative pathological reports on 139 laryngo-pharyngeal cancer lesions were retrospectively reviewed, and the association between macroscopic findings in the lesions and the depth of tumor invasion was analyzed statistically.

Results: The ratios of lesions macroscopically classified as 0-I (superficial and protruding), 0-IIa (slightly elevated), 0-IIb (true flat), 0-IIc (slightly depressed), and 0-III (superficial and excavated) in the preoperative endoscopy reports were 3%, 25%, 71%, 1%, and 0%, respectively. Regarding the depth of tumor invasion in the postoperative pathological reports, the ratios of lesions classified as EP (carcinoma in situ), SEP (tumor invades subepithelial layer), and MP (tumor invades muscularis propria) were 73%, 26%, and 1%, respectively. The ratios of subepithelial invasion or muscular invasion in 0-I, 0-IIa, and 0-IIb were 100%, 54%, and 14%, respectively, and showed significant difference ($P < 0.0001$). Only one of 139 lesions invaded the muscular propria.

Conclusions: This study is the first one to show that macroscopic findings by ME-NBI predict the depth of tumor invasion in superficial laryngo-pharyngeal cancer. It was indicated that there is a little chance of muscular invasion if the lesion is endoscopically diagnosed as 0-I or 0-II. A new T stage classification based on the depth of tumor invasion may be needed in order to adapt the classification to include transoral surgery.

Key Words: Magnifying endoscopy, narrow band imaging, endoscopic laryngo-pharyngeal surgery, transoral robotic surgery, TNM classification.

Level of Evidence: 4

***Laryngoscope*, 00:000–000, 2014**

INTRODUCTION

Transoral surgery is a less invasive treatment that is becoming a major strategy in the treatment for laryngo-pharyngeal cancer. Since the 1990s, transoral laser microsurgery (TLM) has been recognized as an organ preservation strategy that reportedly has good oncological control and functional results,[1] although it has not been widely used because of its technical difficulty. Recently, transoral robotic surgery (TORS) is becoming popular as a new treatment modality for laryngo-pharyngeal cancer, and surgical robots are widely used in the United States.[1] To date, several methods have been reported as less invasive transoral surgical approaches, such as TLM, TORS,[2–4] and transoral videolaryngoscopic surgery.[1] These surgical methods have great advantages over the conventional open surgery, especially in functional outcomes such as swallowing and use of voice, and are creating a paradigm shift in the treatment strategy for laryngo-pharyngeal cancer.

One of the most important factors for achieving success in transoral surgery is the ability to determine properly whether there is indication for transoral surgery and especially the ability to estimate the depth of tumor invasion precisely at the preoperative examination. Cancer lesions that invade bone or cartilage are contraindications for this technique. In addition, the preoperative estimation of the depth of tumor invasion strongly influences functional outcomes, such as swallowing and use of voice, whereas the extent of resection in the laryngo-pharynx directly affects swallowing and

Additional Supporting Information may be found in the online version of this article.

From the Department of Otolaryngology–Head & Neck Surgery (I.T., S.H., M.K., S.I., Y.K., J.I.); the Department of Gastroenterology and Hepatology (SHUKO M., SHIN'ICHI M.); the Department of Clinical oncology (M.M., T.H.); and the Department of Biomedical Statistics and Bioinformatics (SATOSHI M.), Graduate School of Medicine, Kyoto University, Kyoto, Japan, and King ChulalongKorn Memorial Hospital (P.M.), Thailand.

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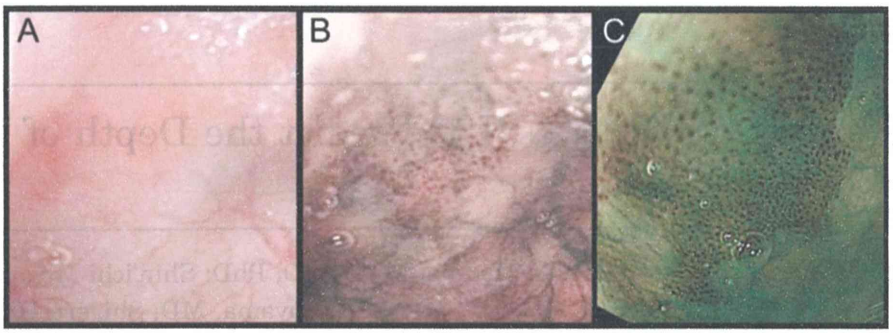

Fig. 1. The same superficial cancer lesion in the hypopharynx observed by endoscope for otolaryngology (ENF type VQ) with white light (A), endoscope for otolaryngology (ENF type VQ) with NBI (B), and magnifying endoscope for upper gastrointestinal tract (GIF TYPE H260Z) with NBI (C). (A) The lesion cannot be identified by ENT endoscope with white light. (B) The lesion can be identified by ENT endoscope with NBI, although the contrast is poor. (C) The lesion is clearly identified as a brownish area with scattered dots of abnormal vessels, and the margin of the lesion is easily traceable. ENT = ear, nose, and throat; NBI = narrow band imaging.

voice functions. Although computed tomography and magnetic resonance imaging are widely accepted as useful modalities for estimating the extent of tumor growth, different preoperative invasion staging techniques may help estimating the depth of tumor invasion more accurately. Therefore, developing a method to predict the depth of tumor invasion is needed in transoral surgery.

Narrow band imaging (NBI) is an innovative optical technology that can increase contrast of the precise morphological changes in the mucosal surface. When combined with magnifying endoscopy, NBI clearly visualizes microvascular structures.[5] In the head and neck region, we have previously reported that magnifying gastrointestinal endoscopy with NBI function (ME-NBI) provides high-resolution images and is useful in detecting early superficial laryngo-pharyngeal cancers, which are difficult to detect by standard endoscopy.[6–8] In addition to the detection, ME-NBI is useful in predicting the depth of tumor invasion in the upper gastrointestinal tract.[9] For example, esophageal cancer is classified in detail in terms of macroscopic morphology and the pathological depth of tumor invasion according to the Japanese Classification of Esophageal Cancer (10th edition),[10] and correlations between endoscopic findings and the depth of tumor invasion have been reported.[11] Nevertheless, although Kikuchi et al.[12] reported correlation between microvascular characteristics and the depth of tumor invasion in superficial pharyngeal cancer, no reports have been published regarding the correlation between macroscopic findings and the depth of tumor invasion in head and neck cancer.

Since 2007, the departments of otolaryngology head and neck surgery and gastroenterology and hepatology in our university hospital have been collaborating and have been screening the laryngo-pharyngeal region of all patients who have a history of esophageal cancer or head and neck cancer by using ME-NBI. Detected lesions were macroscopically classified and were then biopsied. If a lesion was diagnosed as superficial cancer, it was treated by either endoscopic submucosal dissection (ESD)[13,14] or endoscopic laryngo-pharyngeal surgery (ELPS), which was developed to treat laryngo-pharyngeal superficial cancer.[15]

The purpose of this study is to examine if the preoperative macroscopic classification with ME-NBI is useful in predicting pathological depth of tumor invasion in laryngo-pharyngeal cancer. Endoscopic report data on the screening and postoperative pathological results were retrospectively reviewed, and the correlation between the macroscopic endoscopic classification and the pathological depth of tumor invasion was statistically analyzed.

MATERIALS AND METHODS

Patients and Lesions

During the period from February 2007 to January 2014, 176 consecutive laryngo-pharyngeal lesions in 106 patients were treated with ELPS or ESD under general anesthesia at Kyoto University Hospital, Japan. Among them, 139 fresh lesions of carcinoma in situ or squamous cell carcinoma in 91 patients who had no history of radiation therapy to the neck or surgery to the same site are included in this study. The 15 patients excluded from the study include four patients with a history of surgery on the same site, four with a history of neck radiation, one with a spindle cell carcinoma, and six with nonmalignant lesions.

Patients were predominantly male (86 cases, 95%) and the median age was 67 years (range 33–85 years). Written informed consent for the treatment was obtained from all patients; and this study was approved by the institutional review board of the Graduate School of Medicine, Kyoto University.

Macroscopic Classification by Magnifying Endoscopy With Narrow Band Imaging

All procedures were performed using a ME-NBI (GIF TYPE H260Z, Q240Z, or Q260J; Olympus Medical Systems, Tokyo, Japan), as reported previously.[5] In short, each patient was sedated with 35-mg pethidine hydrochloride before the examination. A nonmagnifying observation with NBI was performed to identify abnormal mucosal areas. If abnormal mucosal areas (e.g., well demarcated brownish lesions) were identified, photographs of the nonmagnified NBI view were taken. Subsequently, the lesion and surrounding normal mucosa was observed under magnification. ME-NBI has the capabilities of both standard video endoscopy and adjustable image magnification over a continuous range up to a magnification factor of 80, and it provides higher resolution images with higher

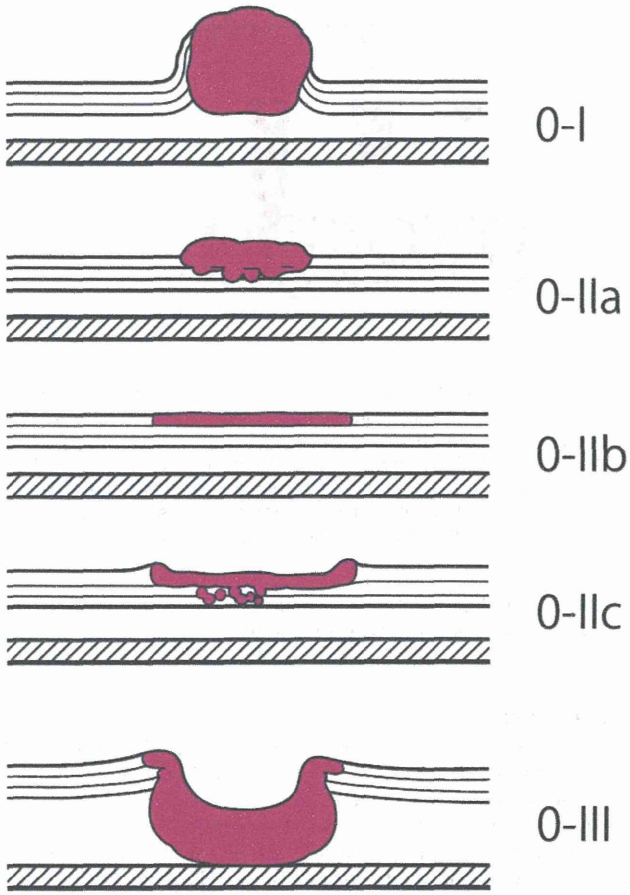

Fig. 2. Schematic view of the macroscopic classification of superficial esophageal cancer in the Japan Classification of Esophageal Cancer (10th edition), modified from reference 10. This classification is applied for head and neck cancer in the General Rules for Clinical Studies on Head and Neck Cancer (5th edition) of the Japan Society for Head and Neck Cancer[17] and used for this study. 0-I (superficial and protruding type: more than 1 mm in height), 0-IIa (slightly elevated type: less than 1 mm in height), 0-IIb (flat type), 0-IIc (slightly depressed type: less than 0.5 mm in depth), 0-III (superficial and excavated type). [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

contrast compared to endoscopes with NBI used in otolaryngology, such as ENF-VQ and ENF-VH (Olympus Medical Systems) (Fig. 1).

If scattered brownish dots were observed within the lesion under ME-NBI, the lesion was clinically diagnosed as malignant, as has previously been reported for lesions in the esophagus.[16] Biopsy was performed to pathologically confirm the malignancy after the observation.

Macroscopic morphology of the lesion was classified quickly after the examination and reported in accordance with both the Japanese Classification of Esophageal Cancer (10th edition)[10] and the General Rules for Clinical Studies on Head and Neck Cancer (5th edition) of the Japan Society for Head and Neck Cancer[17] by at least two experienced gastroenterologists who had no information regarding the pathology. According to the Japanese Classification of Esophageal Cancer (10th edition),[10] superficial cancer is defined as a lesion with no invasion to the muscularis propria, and tumors in which invasion is diagnosed to extend to the muscularis propria or beyond are classified as advanced type. The superficial type has the prefix *0* and is classified into 0-I (superficial and protruding type), 0-II (superficial and flat type), or 0-III (superficial and excavated type). Type 0-II (superficial and flat type) is classified into 0-IIa (slightly elevated type: less than 1 mm in height), 0-IIb (true flat type), and 0-IIc (slightly depressed type). The utility and clinical relevance of the Japanese endoscopic classification of superficial neoplastic lesions of the gastrointestinal (GI) tract, including esophagus, stomach, and colon, were explored by an international group of endoscopists, surgeons, and pathologists in an intensive workshop in Paris in 2002, and the results[9] were published in 2003. This endoscopic classification of the GI tract is globally accepted and is also called the Paris endoscopic classification.[9] Clinically, the height and depth of a lesion are evaluated by placing a single cup of the opened biopsy forceps (approximately 1.2 mm in height) next to the lesion as a calibrating gauge. Lesions protruding above the level of the cup are classified as 0-I; and protruding lesions that have a thick pedicle with a broad base[18] and restricted mobility are classified as type 1, an invasive tumor. Lesions that are depressed by more than half the level of a single cup are classified as 0-III. Entirely flat lesions with neither protrusion nor depression observed with ME-NBI are classified as 0-IIb. The 0-IIb lesions are detectable only with NBI. This classification has been applied for head and neck cancer by the Japan Society for Head and Neck Cancer as the General Rules for Clinical Studies on Head and Neck Cancer (5th edition).[17] Schema views of each of the subtypes of the superficial cancer are shown in Figure 2.

Surgical Procedure

If the lesion was clinically diagnosed as superficial cancer, ELPS or ESD was indicated as a minimally invasive treatment under general anesthesia. ELPS was developed to treat laryngopharyngeal superficial cancer. The concept of ELPS is the same as that of ESD in that both are performed as en bloc resection of a cancer lesion following submucosal injection, but it differs from ESD in that the resection procedure is performed by a head and neck surgeon with both hands (Supp. Fig. S1). After starting the use of ELPS in August 2009, all lesions have generally been treated with ELPS except those that invaded the cervical esophagus beyond the entrance of the esophagus. In brief, a curved rigid laryngoscope (Nagashima Medical Instruments Company, Ltd, Tokyo, Japan) was inserted to provide a working space in the pharyngeal lumen, and a ME-NBI was inserted transorally by a gastroenterologist to visualize the surgical field (Supp. Fig. S2). The extent of the lesion and the exact margins were determined by NBI and iodine staining. A mixed solution of epinephrine (0.02 mg/mL) and saline was injected into the subepithelial layer beneath the lesion in order to lift the lesion above the surrounding mucosa and to create a safety space. Specially designed curved forceps[13] (Nagashima Medical Instruments Company, Ltd, Tokyo, Japan) and a curved electrosurgical needle knife (Olympus Medical Systems) were orally inserted and the tumor was resected. Thirty-five lesions were treated with ESD, and 104 lesions were treated with ELPS in this study.

Pathology and Evaluation of the Invasion of the Tumor

All resected specimens were cut into longitudinal slices 2 mm in width after fixation. The slices were embedded in paraffin and stained with hematoxylin-eosin. All specimens were microscopically evaluated according to the World Health Organization Classification. T staging was performed according to the Union for International Cancer Control tumor-node-

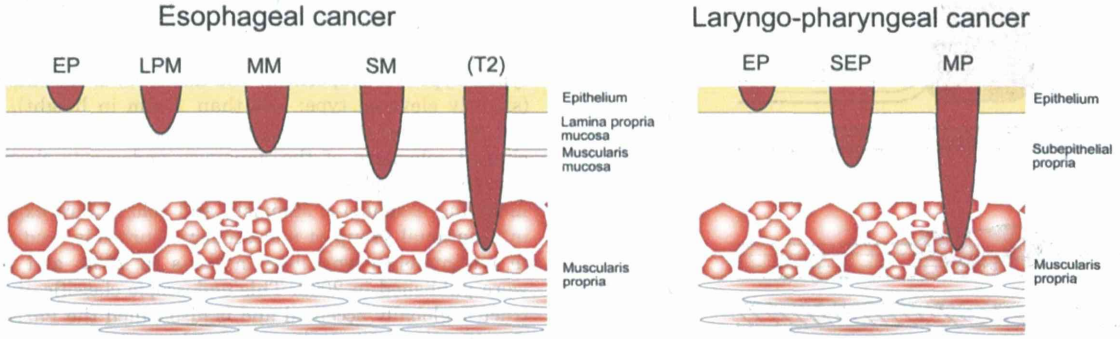

Fig. 3. Schematic view of the pathological classification for the superficial cancer of the esophageal cancer and the head and neck cancer, in the Japan Classification of Esophageal Cancer (10th edition)[10] and the General Rules for Clinical Studies on Head and Neck Cancer (5th edition) of the Japan Society for Head and Neck Cancer,[17] respectively, modified from reference 10.
In the esophageal cancer, superficial cancers are classified as EP (carcinoma in situ), LPM (tumor invades lamina propria mucosa), MM (tumor invades muscularis mucosa), and tumor invades submucosa (T1b), depending on the depth of tumor invasion. In the laryngo-pharynx, because muscularis mucosa is absent in the laryngo-pharynx, the lesion was classified as EP (carcinoma in situ), SEP (tumor invades subepithelial layer), and MP (tumor invades muscularis propria).[17] [Color figure can be viewed in the online issue, which is available at www.laryngoscope.com.]

metastasis (UICC/TNM) classification (7th edition) of the head and neck cancer.[19]

Evaluation of the invasion of the tumor was also made according to the General Rules for Clinical Studies of Head and Neck Cancer (5th edition) by the Japan Society for Head and Neck Cancer[17] and the Japanese Classification of Esophageal Cancer by the Japan Esophageal Society (10th edition).[10]

In the esophageal cancer, superficial cancers are pathologically classified as EP (carcinoma in situ), LPM (tumor invades lamina propria mucosa), MM (tumor invades muscularis mucosa), and tumor invades submucosa (T1b), depending on the depth of tumor invasion.[10] In the laryngo-pharynx, because muscularis mucosa is absent in the laryngo-pharynx, the lesion was classified into EP (carcinoma in situ), SEP (tumor invades subepithelial layer) and MP (tumor invades muscularis propria), according to the General Rules for Clinical Studies on Head and Neck Cancer by the Japan Society for Head and Neck Cancer (5th edition).[17] In this study, all lesions were classified as EP, SEP, or MP in accordance with the rule by the Japan Society for Head and Neck Cancer.[17] Schematic views of pathological classification of the depth of tumor invasion in the esophageal cancer and head and neck cancer are shown in Figure 3.

TABLE I.
Lesion Characteristics.

Origin	Subsite	
Oropharynx	Anterior wall	5
	Posterior wall	19
	Superior wall	9
	Lateral wall	8
Hypopharynx	Piriform sinus	76
	Post cricoid	3
	Posterior wall	16
Larynx	Supraglottic	3
T stage		
Tis	101	
T1	16	
T2	18	
T3	4	

Data Analysis

Macroscopic classification with a ME-NBI, pathological classification regarding the depth of tumor invasion, lymphatic invasion, vessel invasion, and recurrence was reviewed. The association between macroscopic classification (0-I /0-IIa/0-IIb) and the depth of tumor invasion (EP/SEP + MP) was statistically analyzed using the Cochran–Mantel–Haenszel test (degree of freedom = 1). Because of the small sample size (N = 1), 0-IIc was excluded from the statistical analysis. SAS for Windows 9.3 (SAS Institute Inc., Cary, NC) was used for the analysis.

RESULTS

Lesion characteristics are shown in Table I. Of the 139 lesions resected, the total number of lesions in the oropharynx, hypopharynx, and larynx was 41 (30%), 95 (68%), and three (2%), respectively. In the oropharynx, the numbers of lesions in the anterior, posterior, superior, and lateral walls were five (12%), 19 (46%), nine (22%), and eight (20%), respectively. In the hypopharynx, the numbers of lesions in the piriform sinus, post-cricoid, and posterior walls were 76 (80%), three (3%), and 16 (17%), respectively. In the larynx, all lesions were in the supraglottic area. Regarding the T classification, 101 lesions were pathologically diagnosed as Tis, 16 lesions as T1, 18 lesions as T2, and four lesions as T3.

Macroscopic classification, pathological classification regarding the depth of tumor invasion, lymphatic invasion, vessel invasion, and the number of recurrences are shown in Table II. The numbers of lesions classified macroscopically as 0-I, 0-IIa, 0-IIb, 0-IIc, and 0-III were 4 (3%), 35 (25%), 99 (71%), one (1%), and 0(0%), respectively. Representative images of each subtype are shown in Figure 4. Regarding the depth of tumor invasion, the numbers of lesion classified as EP, SEP, and MP were 101 (73%), 37 (26%), and one (1%), respectively.

In the 0-I lesions, all lesions showed subepithelial invasion (SEP). In the 0-IIa lesions, 18 lesions (51%) were SEP;

TABLE II.
Macroscopic Classification by Magnifying Endoscope, Pathological Classification Regarding the Depth of Tumor Invasion, Lymphatic Invasion, and Vessel Invasion.

		Pathology				
		Depth of Tumor Invasion				
Preoperative Macroscopic Classification	Number of Lesions	EP	SEP	MP	ℓy (+)	v (+)
0-I	4	0	4	0	0	0
0-IIa	35	16	18	1	2	1
0-IIb	99	85	14	0	0	0
0-IIc	1	0	1	0	1	0
0-III	0	0	0	0	0	0

Preoperative Macroscopic Classification	Ratio of SEP + MP*
0-I	100%
0-IIa	54%
0-IIb	14%

*The ratios of SEP + MP in 0-I, 0-IIa, and 0-IIb showed significant difference ($P < 0.0001$; Cochran–Mantel–Haenszel test: degree of freedom = 1).

one lesion (3%) was MP; and vessel invasion was observed in three lesions (9%). In the 0-IIb lesions, most lesions (86%) were EP and there was no vessel invasion. Only one lesion was classified as 0-IIc; and the lesion was pathologically classified as SEP with lymphatic duct invasion.

The ratios of subepithelial invasion or muscular invasion (SEP + MP) in 0-I, 0-IIa, and 0-IIb were 100%, 54%, and 14%, respectively, and showed significant difference ($P < 0.0001$).

DISCUSSION

The present study showed strong correlation between macroscopic classification by ME-NBI and pathological depth of tumor invasion. This is the first report to show that macroscopic findings by ME-NBI predict the depth of tumor invasion in superficial laryngopharyngeal cancer.

Correlations between endoscopic macroscopic type and invasion depth have been reported for superficial esophageal squamous cell carcinoma and early gastric and early colorectal adenocarcinomas in the Paris endoscopic classification,[9] which was made based on the Japanese endoscopic classification of superficial neoplastic lesions of the GI tract. In the multicenter analysis of superficial esophageal squamous cell carcinoma conducted in Japan on the basis of 2,418 patients from 143 institutions,[20] the total risk for submucosal invasion is high (90%) in type 0-I lesions. The highest risk occurs in type 0-I and in type 0-III lesions, and the lowest risk is in type 0-IIb lesions. Ratios of invasion deeper than EP in 0-I, 0-IIa, 0-IIb, and 0-IIc were 99% (259/262), 89% (270/303), 47% (104/221), and 80% (567/707), respectively. In our study, the highest risk for subepithelial invasion occurred in type 0-I (100%); and the lowest risk was in type 0-IIb lesions (14%), which were similar to the results in esophageal cancer.

The major difference between our study and the report on esophageal cancer is the overall ratio of submucosal (muscularis propria) invasion in 0-I and 0-II lesions. The overall ratio of invasion to muscularis propria in 0-I and 0-II lesions in our study was only one of 139 lesions, whereas it was 52% in esophageal cancer.[20] We suggest that one reason for this discrepancy may be associated with the different populations. For example, in our study there was just one 0-IIc lesion, but the ratio of 0-IIc in esophageal cancer was 47%. Although it is unclear if the population difference is due to a natural characteristic of laryngo-pharyngeal cancer or to an institutional bias, the results indicate that there is a little chance of muscular invasion in the laryngo-pharyngeal cancer as long as the lesions are diagnosed as 0-I and 0-II.

Finally, the correlation between macroscopic morphological classification and the depth of tumor invasion shown in this study may contribute to modify the T stage classification in head and neck cancer. The T stage classification of head and neck cancer, especially in the pharynx, is based on the diameter of the tumor. This is probably because radiotherapy or open neck surgery are two standard modalities, and the volume or the area of the tumor are important for them. The T staging system is the gold standard in evaluating a primary lesion and its prognostic importance is widely accepted. However, the limitation of the current T staging system is becoming evident with the development of new treatments and diagnostic modalities. For example, NBI enables detection of superficial pharyngeal cancer lesions that are barely visible by conventional methods, and excellent long-term oncological outcome for endoscopic resection of such lesions is reported with the 5-year cause-specific survival rate of 97%.[13] According to the current T staging system, a pharyngeal superficial cancer with micro invasion, such as SEP, is diagnosed as T3 when it is