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From 29th November to 01st December 2017

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Preface

The XXth annual conference of Cancer prevention was held by Vietnamese Cancer Society in collaboration with HCMC Oncology Hospital and HCMC Cancer Society.

This conference took place from 29th November to 01st December 2017. Beside all topics about diagnosis, treatment, early detection and prevention, this year, the scientific program included many topics related to modern techniques in Radiotherapy and Breast cancer therapy presented by well-known specialists from USA, Australia, Japan, Taiwan, Singapore...

We gratefully acknowledge the permission of authors who agreed to publish their researches in English. We would like to thank HCMC Oncology Hospital for their contribution and help - without them, we would not have been able to organize this great meeting.

Looking forward to receiving cordial comments of colleagues.

On behalf of executive Committee of Vietnamese Cancer Society, I'd like to wish you and your family a very Happy New Year 2018.

HCM city, 04 December 2017

Director of HCMC Oncology Hospital

Pham Xuan Dung, MD, PhD.

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CONTENTS

EVALUATION OF EFFICACY OF TISSUE AUTOFLUORESCENCE IMAGING IN THE DIAGNOSIS OF ORAL CANCER

DANG HUY QUOC THINH[1], TRAN MINH CUONG[2], TRAN NGOC LIEN[2],
NGUYEN PHAN THE HUY[2], NGUYEN DUC TUAN[2], NGUYEN THI HONG[2]

ABSTRACT

Background: *Normal oral mucosa emits a pale green autofluorescence while abnormal tissue may show loss of autofluorescence and appears dark in contrast. Loss of autofluorescence as an early phenomenon associated with tissue degeneration seems to be promising for the diagnosis of oral cancer.*

Objective: *To assess the value of tissue autofluorescence imaging in the diagnosis of oral cancer.*

Materials and methods: *The cross-sectional study was conducted on 133 patients with non-healing oral mucosal lesions. After oral examination under white light, the tissue autofluorescence imaging using VELscope® was applied. All the lesions were biopsied for definitive diagnosis. The diagnostic values were calculated for the autofluorescence imaging compared to histopathological diagnosis.*

Results: *In total there were 133 oral mucosal lesions, among them 107 malignant ones (80.5%) and 26 benign ones (19.5%). The autofluorescence imaging displayed high sensitivity of 90.7% and average specificity of 46.2%. The accuracy of this test was 82.0%. The positive predictive value was 87.4% and the negative predictive value 54.5%. The area under the curve (AUC) was 0.68. The Kappa coefficient was 0.4, which showed a moderate agreement between autofluorescence imaging and histopathology.*

Conclusion: *As a simple and non-invasive technique, with high sensitivity, the tissue autofluorescence test could be a useful diagnostic adjunct to visual inspection for the detection and localization of oral cancer lesions. However, autofluorescence results must be interpreted with caution and cannot replace conventional histopathological examination.*

Keywords: tissue a*utofluorescence imaging;* o*ral* cancer; *diagnostic value*.

INTRODUCTION

Oral cancer ranks as one of the most common malignancy worldwide. More than 90% of oral cancers are squamous cell carcinoma (OSCC), which is usually preceded by premalignant lesions[26]. Despite better understanding of the disease process and therapeutic advances, the five-year survival rate for oral cancer has remained at approximately 50% over the past three decades[26]. High morbidity and mortality rates call for early detection and treatment of oral potentially malignant disorders and OSCC.

A conventional oral examination has long been the standard method for the detection of oral mucosal abnormalities. However, conventional clinical examination is a poor discriminator of oral mucosal lesions, thereby resulting in delayed patient referral and poorer prognosis[5]. These findings have driven the development of new technologies to assist clinicians for early diagnosis of oral potentially malignant disorders and OSCC.

Visually Enhanced Lesion Scope (VELscope®) is a simple, non-invasive, handled device that emits a blue light (400-460nm) into the oral cavity, which excites biofluorophores in the oral mucosa resulting in a pale green autofluorescence imaging through the selective (narrow-band) filter[5]. Abnormal tissue associated with loss of autofluorescence appears dark in contrast to the surrounding area[10,22]. Rana et al. (2012) showed that the autofluorescence examination using the VELscope® lead to higher sensitivity (100% vs. 17%), but to a lower specificity

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(74% vs. 97%) compared with conventional oral examination[23].

High sensitivity of the tissue autofluorescence imaging was observed in most of studies, such as 100% (Moro et al. 2010[17]; Scheer et al. 2011[24]; Rana et al. 2012[23]), 98% (Lane et al. 2006[10]; Hanken et al. 2014[7]). However, low sensivity was found in some studies, such as 30% in detecting 24 dysplasias and one OSCC (Farah et al. 2012[5]), 50% in detecting 11 dysplasias and one OSCC (Mehrotra et al. 2010[16]). Overall, the sensitivity of autofluorescence imaging was usually reported in detecting oral cancer together with oral potentially malignant disorders in the wide range of 30-100% and 15-81%, respectively[2]. Therefore, the aim of this study was to assess the diagnostic value of tissue autofluorescence imaging for the detection of oral cancer only.

MATERIALS AND METHODS

Patients

133 patients with non-healing oral mucosal lesions were examined at the University of Medicine and Pharmacy and the Oncology Hospital at Ho Chi Minh City from September 2015 to September 2017.

Methods

Following medical history taking and conventional oral examination under white light, a clinical diagnosis was recorded. Clinical examination was repeated using VELscope® (LED Dental, Vancouver, British Columbia, Canada) under the dimmed room light. The VELscope® is a portable device comprising a light source and a filter that allows for directly viewing autofluorescence of the oral mucosa. Lesions that showed loss of autofluorescence were considered to be positive, and those that did not were deemed negative. This assessment involved a comparison of the lesion site with both adjacent tissue and with tissue on the contralateral side as an anatomical control. White light and fluorescence photography of all lesions were performed using an photography camera (Canon PowerShot ELPH130IS). The results were evaluated by two standardized oral specialists with a final agreement.

All patients underwent biopsy. Biopsy specimens were fixed in formalin, blocked in paraffin, stained with hematoxylin-eosin, and assessed by pathologists.

Sensitivity, specificity, accuracy, positive predictive value (PPV) and negative predictive value (NPV) were calculated for the autofluorescence imaging compared to histopathological diagnosis as the gold standard[18]. The 95% confidence intervals (CI) of these values and the area under the curve (AUC) analysis were also reported. Statistical correlations were analyzed using Fisher's exact test. A p-value <0.05 was considered significant.

RESULTS

Clinical and histopathological features

In total of 133 patients, there were 107 patients (80.5%) with the histopathological diagnosis as malignant and 26 patients (19.5%) with benign lesions. Concerning gender and age, there were 101 males (75.9%) and 32 females (24.1%); 47.4% were aged between 40 to 59 years old.

In 108 oral cancer patients, there were 86 males (80.4%) and 21 females (19.6%). Most of them were over 40 (89.7%). The cancer sites were tongue (59.8%), mouth floor (15%), gingiva (7.5%), buccal mucosa (5.6%), lips (4.7%), hard palate (4.7%) and retromolar mucosa (2.7%). The clinical patterns included exophytic type (61.7%) (alone 34.6% or combined with ulcerative 27.1%), ulcer type (31.8%), submucosal type (6.5%). According to TNM classification (UICC, 2016), 26.2% were at T1, 37.4% at T2, 17.7% at T3 and 18.7% at T4 stage. The histopathology confirmed 101 OSCC cases (93.5%) including 63 grade 1 cases (58.3%), 36 grade 2 cases (33.3%) and only two grade 3 cases (1.9%); 6 cases of minor salivary carcinoma (5.6%) including 4 mucoepidermoid carcinomas (3.7%) and 2 adenoid cystic carcinomas (1.9.4%).

In 26 patients having benign lesions, there were 7 fibrous lesions (26.9%), 6 leukoplakias (23.1%), 6 inflammatory lesions (23.1%), 4 papillomas (15.4%) and 3 benign salivary gland tumors (11.5%) (Table 1). These lesions occurred at hard palate (42.3%), buccal mucosa (26.9%), gingiva (11.5%), tongue (7.7%), retromolar mucosa (7.7%) and lips (3.8%).

Table 1. *Characteristics of oral benign lesions based on age, gender and lesion sites*

Variable	Total cases	Benign lesions					p
		(1)	(2)	(3)	(4)	(5)	
Gender							0.523
Male	15	6	3	3	2	1	
Female	11	1	3	3	2	2	
Age							0.589
<40	4	1	2	0	1	0	
40-59	9	2	2	1	2	2	
≥60	13	4	2	5	1	1	
Site							0.357
Lips	1	0	0	1	0	0	
Buccal	7	1	3	2	1	0	
Tongue	2	1	1	0	0	0	
Gingiva	3	1	2	0	0	0	
Palate	11	3	0	2	3	3	
Retromolar	2	1	0	1	0	0	
Total	**26**	**7**	**6**	**6**	**4**	**3**	

1) Fibrous lesions; (2) Inflammation; (3) Leukoplakia; (4) Papilloma; (5) Pleomorphic adenoma

Autofluorescence imaging

The autofluorescence imaging results of these 133 cases showed 111 positive cases (83.5%) and 22 negative cases (16.5%).

Among 107 cancer lesions, 97 positive cases (90.7%) (Figure 1), due to fluorescence visualization (FV) loss, appeared as dark color or black, homogenous or non-homogenous, usually with well-defined margins (partially or totally).

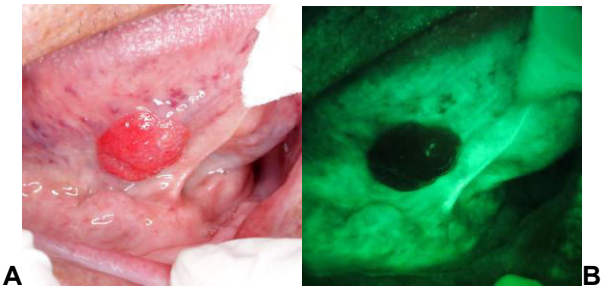

Fig. 1. *An early tongue squamous cell carcinoma (A) showed loss of autofluorescence (B).*

However, there were 10 oral cancer cases having false negative result, accounting for 9.3% of cancer lesions. Notably, there was no significant difference in the false negative prevalence between men and women, among age groups, primary tumor sites, patterns, stages and histopathological features (p>0.05) (Table 2).

***Table 2**. Association between clinical and autofluorescence features of oral cancer lesions*

Variable	Oral cancer lesions (n=107)			p
	Total	FV (n=10) cases (%)	FV loss (n=97) cases (%)	
Gender				0.683
Male	86	9 (10.5)	77 (89.5)	
Female	21	1 (4.8)	20 (95.2)	
Age				0.495
<40	11	2 (18.2)	9 (81.8)	
40-59	54	5 (9.3)	49 (90.7)	
≥ 60	42	3 (7.1)	39 (92.9)	
Site				0.405
Lips	5	2 (40.0)	3 (60.0)	
Buccal	6	0 (0)	6 (100.0)	
Tongue	64	7 (10.9)	57 (89.1)	
Mouth floor	16	1 (6.3)	15 (93.7)	
Gingiva	8	0 (0)	8 (100.0)	
Hard palate	5	0 (0)	5 (100.0)	
Retromolar	3	0 (0)	3 (100.0)	
Pattern				0.082
Exophytic	66	7 (10.6)	59 (89.4)	
Ulcerative	34	1 (2.9)	33 (97.1)	
Submucosal	7	2 (28.6)	5 (71.4)	
Stage				0.853
T1	28	2 (8.1)	26 (91.9)	
T2	40	5 (8.0)	35 (92.0)	
T3	19	2 (10.5)	17 (90.5)	
T4	20	1 (5.0)	19 (95.0)	
Histopathology				0.999
Grade 1 OSCC	63	6 (9.5)	57 (90.5)	
Grade 2 OSCC	36	4 (11.1)	32 (88.9)	
Grade 3 OSCC	2	0 (0)	2 (100.0)	
Salivary carcinoma	6	0 (0)	6 (100.0)	

Loss of autofluorescence was found in 14 benign lesions, accouting for 53.8% of benign lesions (Figure 2). Nearly half of those were inflammation lesions (42.9%) such as lichen, traumatic ulcer, and the remains were pleomorphic adenomas (21.4%), leukoplakias (21.4%) and papillomas (14.3%). Most of these lesions occurred in buccal mucosa and hard palate (64.3%).

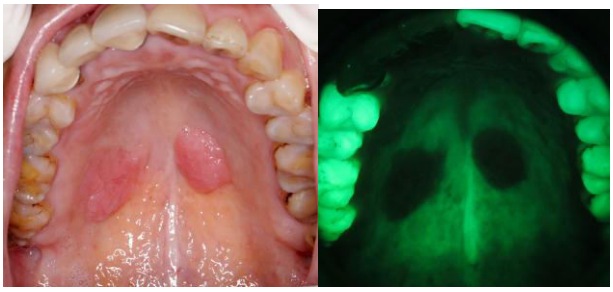

Fig. 2. *Papillomas on the hard palate (A) showed loss of autofluorescence (B).*

On statistical analysis, autofluorescence results were significantly different only in genders ($p<0.05$) and lesion types ($p=0.001$) (Table 3).

Table 3. *Association between clinical and autofluorescence features of oral benign lesions*

Variable	Oral benign lesions (n=26)			p
	Total	FV (n=12) cases (%)	FV loss (n=14) cases (%)	
Gender				**0.021**
Male	15	10 (66.7)	5 (33.3)	
Female	11	2 (18.2)	9 (81.8)	
Age				0.765
<40	4	1 (25.0)	3 (75.0)	
40-59	9	4 (44.4)	5 (55.6)	
≥60	13	7 (53.8)	6 (46.2)	
Site				0.700
Lips	1	0 (0)	1 (100.0)	
Buccal	7	2 (28.6)	5 (71.4)	
Tongue	2	1 (50.0)	1 (50.0)	
Gingiva	3	1 (33.3)	2 (66.7)	
Hard palate	11	7 (63.6)	4 (36.4)	
Retromolar	2	1 (50.0)	1 (50.0)	
Lesion types				**0.001**
Fibrous lesion	7	7 (100.0)	0 (0)	
Inflammation	6	0 (0)	6 (100.0)	
Leukoplakia	6	3 (50.0)	3 (50.0)	
Papilloma	4	2 (50.0)	2 (50.0)	
Pleo. adenoma	3	0 (0)	3 (100.0)	

Compared with histopathological diagnosis as gold standard (Table 4), the autofluorescence imaging had a sensitivity of 90.7% (95% CI = 83.5-95.4%), a specificity of 46.2% (95% CI = 26.6-66.6%), an accuracy of 82.0% (95% CI = 74.4-88.1%), a PPV of 87.4% (95% CI = 79.7-92.9%), and a NPV of 54.5% (95% CI = 32.2-75.6%). The AUC was 0.68 (95% CI = 0.58-0.79). The Kappa coefficient was 0.4 which showed a moderate

agreement between autofluorescence examination and histopathological diagnosis.

Table 4. *Results of fluorescence visualization (FV) versus histopathological diagnosis*

		Histopathology		Total
		Positive	***Negative***	
FV	*Positive*	97	14	111
	Negative	10	12	22
Total		**107**	**26**	**133**

DISCUSSION

VELscope® autofluorescence imaging proved to be a convenient (small, light handpiece), simple using, non invasive and quick technique (2 minutes in average to check the overall oral mucosa). In this study, most of intraoral lesions showed loss of autofluorescence (83.5%), especially in oral cancer (90.7%).

The phenomenon of autofluorescence is based on the interaction of various biofluorophores. Biofluorophores have the ability to absorb light, quickly become unstable and release the energy in the form of fluorescence by emitting directly visible fluorescent light in the violet to green region of the spectrum once they get excited by a higher energy light source[5,9,11]. Most of the fluorescence originates from collagen, its cross-links and elastin, which are located in the stroma and basement membrane, and a small fraction originates from reduced nicotinamide adenine dinucleotide (NADH) and flavin adenine dinucleotide (FAD) in epithelial cells[11,21,22]. Changes in the structure (e.g., hyperkeratosis, epithelial thickness, hyperchromatin and increased cellular/nuclear pleomorphism) and metabolism (e.g. concentration of NADH and FAD of epithelial cells), as well as changes of the stroma (e.g. composition of collagen matrix and elastin, and vascularization) can affect absorption and scattering of light that alter their autofluorescence[2,12,21].

In 107 oral cancer cases, most of cancer lesions (90.7%) showed fluorescence visualization loss, with the FV loss: FV ratio being 9:1. The loss of autofluorescence in oral cancer may include the following changes[6,11,20,22]: (1) The fluorescence intensity of collagen decreases because the collagen cross-links are broken down by matrix metalloproteinases during tumor invasion; (2) Increased metabolism during carcinogenesis and invasion causes FAD to fluorescent less; (3) Increased epithelial thickness, increased nuclear size, cancer cell hyperproliferation and decreased apoptosis lead to cell and nuclear crowding; and (4) Blood hemoglobin absorbs light at 420nm and is more abundant during carcinogenesis as a result of increased microvascularization.

However, there were 10 oral cancer cases (9.3%) with false negative result. These autofluorescence cancer lesions were more likely to present in exophytic and submucosal patterns, grade 1 and 2 OSCC although this did not reach significance level (p>0.05). The exophytic pattern and hyperkeratosis showed fluorescence on the surface which limited the visuality of fluorescent loss areas beneath.

In 26 benign mucosal lesions, autofluorescence loss was also found although its prevalence is lower (53.8%) than that in oral cancer, with the FV loss: FV ratio being 1.1:1. The autofluorescence features were significantly associated with gender ($p < 0.05$) and lesion types ($p=0.001$). All 7 fibrous lesions (100%) retained autofluorescence due to collagen fibers increase, and most of them (85%) occured in men. Otherwise, all 6 inflammatory lesions and 3 pleomorphic adenomas (100%) showed autofluorescence loss. The autofluorescence can be lost in the presence of mucosal inflammation, because blood hemoglobin also increases as a result of inflammation, together with altered metabolic activity in inflamed mucosa, is the main confounding factor for fluorescence[10,11]. In pleomorphic adenoma, increasing tumor cells and loose chondromyxoid stroma may contribute to the autofluorescence loss. In papillomas and leukoplakias, increasing epithelial thickness can cause autofluorescence loss.

Overall, the sensitivity of the autofluorescence test using VELscope® ranged from 30% to 100%, the specificity ranged from 15% to 100%. This wide range was largely due to the difference in study sample (oral cancer and/or oral potentially malignant disorders), the inconsistency in criteria to define positive result. Our study demonstrated high sensitivity (90.7%) and PPV (87.4%), average specificity (46.2%) and NPV(54.5%), an acceptable AUC (0.68) and a moderate agreement of Kappa coefficient (0.4). These results were comparable with most of published studies using VELscope® (Table 5). In a Cochrane database systematic review, Macey et al. (2015) reported that the sensitivity was 0.91 (0.77 to 0.97), and specificity was 0.58 (0.22 to 0.87) for light-based detection14.

Table 5. *Effectiveness of tissue autofluorescence imaging for detection of oral cancers and/or oral potentially malignant disorders*

Authors	Lesions n	Sensitivity %	Specificity %
Lane et al 2006[10]	50	98	100
Mehrotra 2010[16]	156	50	39
Moro et al 2010[17]	32	100	93
Awan et al 2011[1]	44	84	15
Scheer et al 2011[24]	64	100	81
Sweeny et al 2011[25]	88	81	50
Farah et al 2012[5]	112	30	63
Marzouki 2012[15]	85	92	77
Rana et al 2012[23]	123	100	74
Hanken et al 2013[7]	60	98	42
Bhatia et al 2014[3]	222	64	54
Tran MC et al 2017	133	91	46

Padeni et al. (2011) showed that VELscope imaging could identify OSCC with a sensitivity of 96% and oral potentially malignant disorders with a sensitivity of 85% in a study of 175 oral mucosa lesions19. With high sensitivity, the autofluorescence imaging could be a helpful method to detect oral cancer and oral potentially malignant disorders.

However, the low specificity could lead to overdiagnosis in clinical practice and unnecessary biopsy. This lack of specificity remains a constant problem in clinical routine use and was also one of the main drawbacks of many studies[8,12,13,23]. Therefore, the results should be interpreted with caution due to the issue of frequently occurring false positive results and this low specificity.

In the non-malignant group, all inflammatory lesions including lichen, lichenoid, traumatic ulcers showed loss of fluorescence. To reduce the false positive results, some authors proposed a three week review to allow for resolution of inflammatory lesions[11]. If they do not resolve, further assessment and biopsy are generally recommended. In short, the results should be interpreted with caution, since benign lesions can also cause the loss of fluorescence. The autofluorescence test should only be used after a thorough clinical examination, since it is not a diagnostic tool but a device to complement the visual and manual inspection, and cannot be a replacement for the gold standard of any histological evaluation[23].

The true value of this autofluorescence imaging will have to be ascertained with longitudinal studies, but the data to date are encouraging. In a systematic review, Carreras-Torrasa et al. (2015) concluded that optical techniques and diagnostic techniques for imaging have proved to be particularly useful, but their results are not yet clinically relevant[4]. There is still no convincing or adequate data to support their efficacy in oral cancer screening in general population especially for early detection or for reducing the death rate from oral cancer.

CONCLUSION

The autofluorescence test is a simple, easy-to-use, non-invasise and rapid examination with high sensitivity in the diagnosis of oral cancer. However, the specificity of this test is not high which demands closed coordination with clinical examination, knowledge and experience of the observers, and cannot be a replacement for the gold standard of any histological evaluation.

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ROBOT-ASSISTED SURGERY IN UROONCOLOGY: INITIAL APPLICATION AT BINH DAN HOSPITAL

NGUYEN PHUC CAM HOANG[3], TRAN VINH HUNG[4], VU LE CHUYEN[2], NGUYEN VAN AN[1], ĐO VU PHUONG[1], NGUYEN NGOC CHAU[1], ĐO ANH TOAN[1], LE TRONG KHOI[1], PHAM HUU ĐOAN1, ĐO LENH HUNG[1]

ABSTRACT

Objectives: *Just recently, the robotic surgery has been applied in Urology for the first time in Vietnam. This paper reports the first 35 cases of robotic radical ablation for urooncological patients using the Robot da Vinci Si ™ system performed at the Department of Urology of Binh Dan Hospital.*

Materials and Methods: *From November 2016 to April 2017, thirty-five robot-assisted radical ablative procedures for urooncological patients, both upper tract and lower tract, were performed using the da Vinci Si™ robot system. The perioperative outcomes were assessed and reported.*

Results: *In 22 cases of robot-assisted prostatectomy: mean age: 66.9 (range: 49–75), operative time: 297 minutues (range: 105-480), pelvic lymphadenectomy: 4/10 cases, neurovascular bundles sparing: 2/10 cases, estimated blood loss (EBL): 355mL (range: 100-1000), postop hospital stay: 6.3 days (range:2-11); In 2 cases of right robot-assisted adrenalectomy (Myelolipoma and Schwannoma): mean age: 37.5 (range: 26-49), operating time: 97.5 minutes (range:45-150), EBL: 75mL (range: 50-100), postop hospital stay: 8 days (range: 4-12); In 2 cases of robot-assisted partial nephrectomy (AML and RCC tumors): mean age: 34 (range: 32-36), operative time: 210 minutes (range: 165-255), EBL: 50mL, warm ischemia time: 15 minutes (range: 10-20), postop hospital stay: 5.5 days (range:5-6); in 3 case of robot-assisted nephroureterectomy for upper tract TCC tumor: age: 54, operative time: 240 minutes, EBL: 800 mL, postop hospital stay: 6 days; In 1 case of robot-assisted radical cystectomy and orthotopic cystoplasty for muscle-invasive tumor: age:45, operative time: 660 minutes, EBL: 500mL, postop hospital stay: 15 days; one conversion to open surgery in robot-assisted radical nephrectomy for right kidney upper pole RCC tumor due to profuse tumoral perirenal invasion and adhesions.*

Conclusions: *Robot-assisted surgery, with many advantages over standard laparoscopic surgery thanks to technological innovations (3D-HD monitor and optical system, robotic arms with wrists, the comfortable console table…) has helped the urologist to perform the sophisticated procedures with shorter learning curves. Our initial series of 35 robot-assisted urooncological procedures has achieved encouraging outcomes. More cases are to be performed in the future.*

Keywords: *Robot-assisted procedures, radical prostatectomy, radical cystectomy, partial nephrectomy, radical nephrectomy, adrenalectomy.*

INTRODUCTION

Robotic surgery is the most advanced achievement in minimally invasive surgical techniques that have been widely available in major surgical centers in developed countries (7). By the end of 2016, for the first time, robotic surgery was applied in adult patients in Vietnam. This article is to report the first 35 cases using the da Vinci SiTM robotic system to perform oncourological procedures in adults patients at the Department of Urology of Binh Dan Hospital.

PATIENTS AND METHOD

Patients

Adult patients suffering from tumors/neoplasm of the urinary tracts at Department of Urology of Binh Dan Hospital who were operated on using the da Vinci SiTM robotic system in the period from 30 November 30th 2016 to April 15th 2017.

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Method

Instrumentation

The robot surgical system da Vinci SiTM with four arms. This system consists of two separate parts connected together ("Master-Slave system").

The tower (Figure 1A): placed over the patient, consisting of 4 robotic arms: 3 arms to hold the surgical instruments and 1 arm to hold a high resolution 3-D camera.

The console (Figure 1B): where the surgeon sits and manipulates the robot joysticks while looking into a stereoscopic display with a high resolution 3-D field, magnified image. The surgeon controls the four robotic arms by using fingers on the joysticks. The surgeon also uses foot pedals to select energy sources (monopole or bipolar)

In addition, the second video screen connected to the bedside assistant with a 2-D image on which the screen shows where the main surgeon is looking at in the operation field.

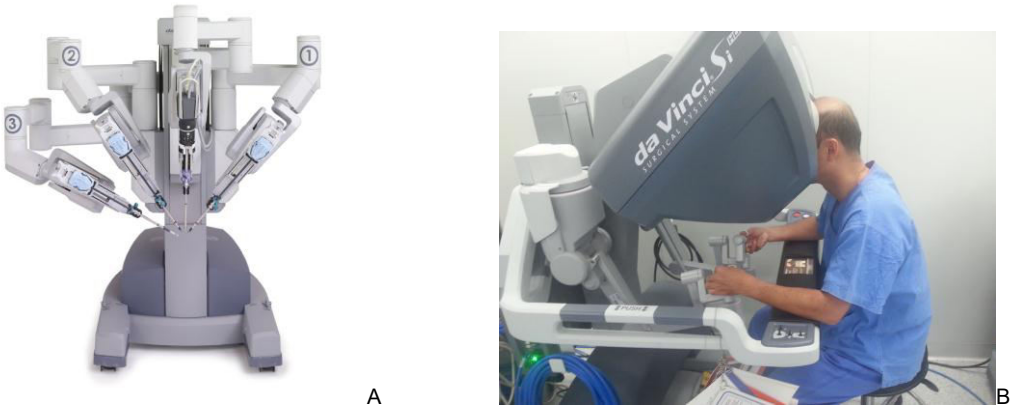


Figure 1. *The robot surgical system da Vinci Si™. A. Tower. B. Console*

The instruments[2]

HotShearsTM monopolar scissors (Fig.2): for dissecting and fulguration

Bipolar MarylandTM Forceps (Fig.3): used for holding, retracting and fulguration in bladder, prostate surgery.

Forceps ProGraspTM (Fig. 4): Non-power instrument having the same characteristics as bipolar fenestrated forceps.

Bipolar fenestrated forceps (Fig.5): used for holding, retracting, blunt dissection, and fulguration in upper tract and kidney surgery.

Big needle holder (Fig.6): for bladder neck – urethra anastomosis, bladder neck reconstruction, peritoneum closure.

Figure 2. *HotShears™ scissors*

Figure 3. *Bipolar Maryland™ Forceps*

Figure 4. *Forceps ProGrasp™*

Figure 5. *Bipolar fenestrated forceps*

Figure 6. *Big needle holder*

Patient positioning and ports placement

Kidney/Upper tract procedures[3]

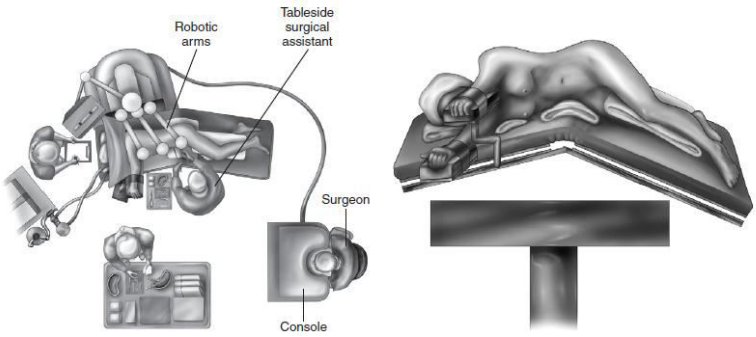


Figure 7. *Operation room and patient positioning*

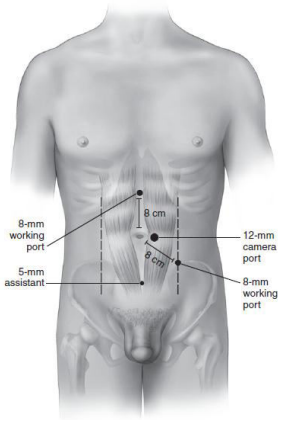


Figure 8. *Ports placement in pyeloplasty[3]*

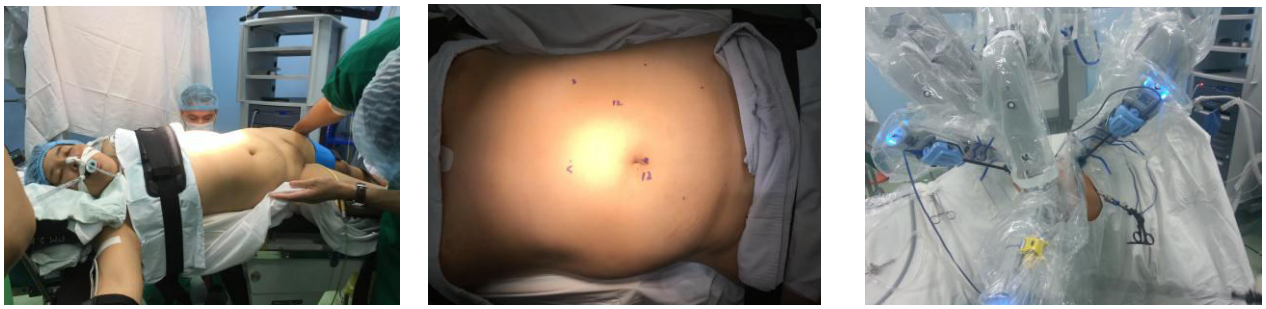


Figure 9. *Patient positioning in pyeloplasty on the left hand side*

Lower tract procedures (prostate, bladder) [2,8]

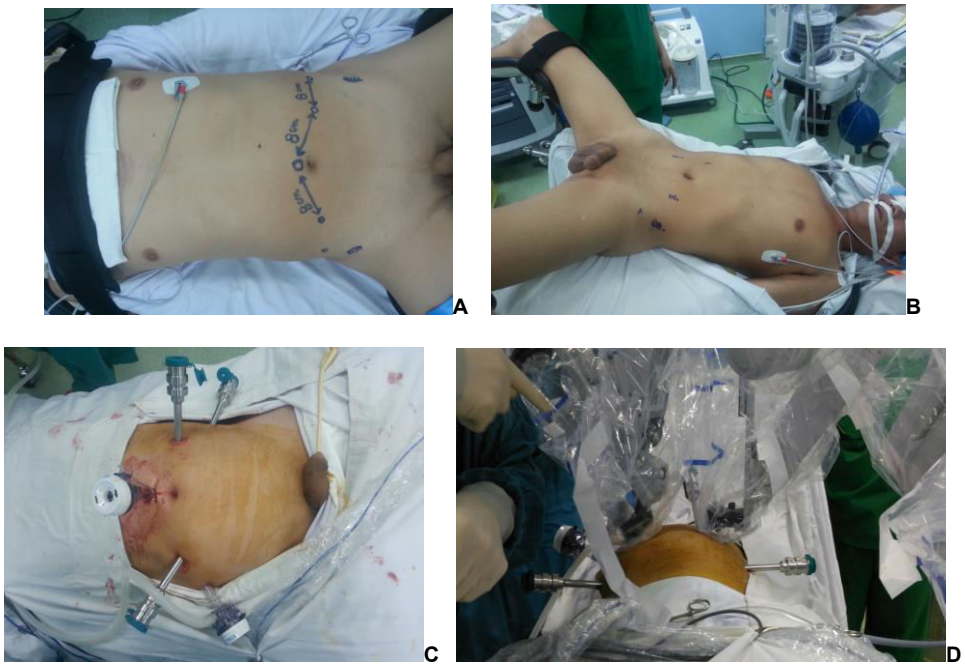


Figure. 10. *Robot-assisted radical prostatectomy. A. Port landmarks. B. Steep Trendelenberg position of 30^0. C. Ports placement. D. Docking*

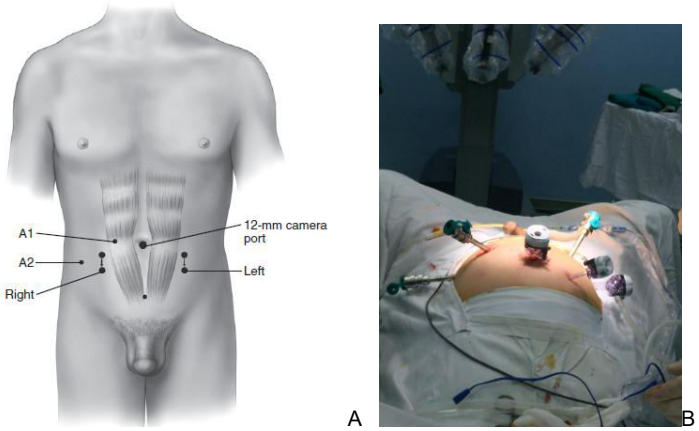


Figure. 11. A.B. Ports placement in robot-assisted radical prostatectomy [8]

RESULTS

From November 30, 2016 to April 15, 2017, thirty-five adults patients suffering from tumors/neoplasm of the urinary tracts underwent radical extirpation surgery by the da Vinci™ robot system: 22 cases of radical prostatectomy for prostate cancer, 6 cases of partial nephrectomy for small renal tumor, 1 case of radical cystectomy + orthotopic extracorporeal ileal neobladder, 2 cases of adrenalectomy, 1 case of radical nephrectomy (conversion to open surgery), 3 cases of radical nephroureterctomy for upper tract transitional cell carcinoma.

22 cases of radical prostatectomy (Fig.12)

Mean age: 66.9 (49-75); ASA score 2: 19 cases, ASA score 3: 3 cases.

Co-morbidity: Arterial hypertension + diabete mellitus: 3 cases; Arterial hypertension: 4 cases.

Mean serum PSA (ng/mL): 32.15 (8.76-93).

Prostate size on MSCT/MRI (mL): 39.46 (31-60).

Preop. Gleason score: 6.4 (4-8); Bone scan: 15/22 cases.

Preop. staging of tumor: T1bNoMo: 2 cases; T2aNoMo: 7 cases; T2bNoMo: 9 cases; T3aNoMo: 2 cases; T3bNoMo: 2 cases. Number of ports: 5 ports: 9 cases; 6 ports: 13 cases.

Operative approach: intraperitoneal (Montsouris technique).

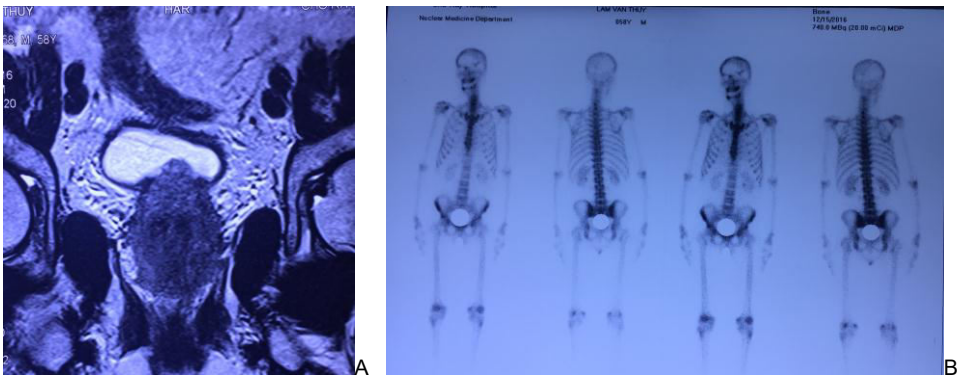
Mean operating time (min.): 297 (105-480); Mean estimated blood loss (mL): 355 (100-1000).

Standard lymphadenectomy: in 8/22 cases; Neurovascular bundle sparing: in 4/22 cases.

Division and suture of the DVC: in 6/22 cases, Suture and division of the DVC: in 16/22 cases; Rocco'stitch: performed in 7/22 cases.

Post-op. drain removal (days): 5.2 (1-10); Postop.hospital stay (days): 6.3 (2-11).

Post-op complications: pelvic fluid collection: in 2/22 cases.



A B

Fig 12. *Patient Lam Van Th., 58YO, PCa, cT3bNoMo. A. Pre-op.MRI. B. Bone scan*

6 cases of patial nephrectomy for small renal tumor (Fig. 13)

Gender: 2 females, 4 males; Mean age: 34 (32-36); ASA score 2: 6 cases.

Mean tumor size (mm): 34 (31-37).

Right tumor: 3 cases; Left tumor: 3 cases.

In 2/6 cases unable to use the 4th arm (for ProGrasp™ forceps) due to fighting between the 3rd arm and the 4th arm.

Mean operating time (min.): 210 (165-255); Mean warm ischemic time (min.): 15 (10-20).

Renal pedicle clamping using: vessel loop: 2 cases; Laparoscopic Bulldog: 4 cases.

Renal parenchymal suturing in two layers: inner layer using V-Loc® 3-0, outter layer using vicryl® 1-0.

Mean estimated blood loss: 50 mL; Mean postop.hospital stay (days): 5.5 (5-6).

Tumor histology: angiomyolipoma: 2 cases, clear cell-renal cell carcinoma (CC-RCC): 4 cases.

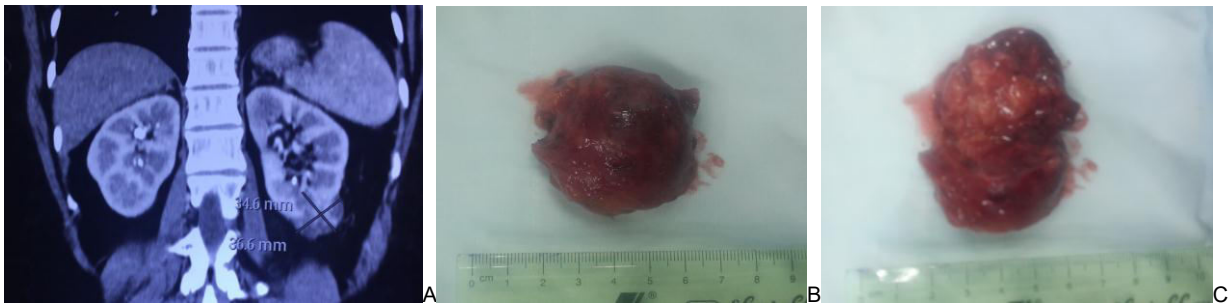


Figure 13. *Small tumor in lower pole of left kidney, CC-RCC. A. MSCT with contrast. B.C. Specimen.*

1 case of radical cystectomy + extracorporeal orthotopic ileal neobladder for muscle invasive bladder tumor (transitional cell carcinoma) (Fig. 14)

Male patien, 45 year old; ASA score: 2, Preop. diagnosis: TCC tumor of bladder cT2bMoMo.

Operative technique: radical cystectomy + extracorporeal orthotopic ileal neobladder (Hautmann).

Number of ports: 6 ports; Operating time (min.): 660; Estimated blood loss (mL): 500.

Postop.hospital stay (days): 15.

Tumor histology: muscle invasive transitional cell carcinoma.

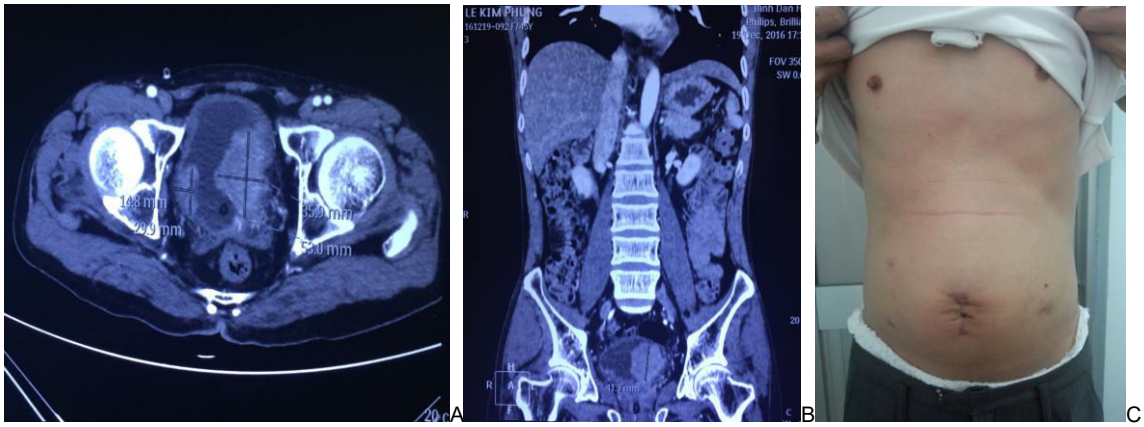


Figure 14. *Muscle invasive bladder tumor. A.B. MSCT with reconstruction. C. Scar in 1 month postop.*

2 cases of right adrenalectomy (Fig. 15)

Gender: 2 females; Mean age: 37.5 (26-49); ASA score 2: 2 cases.

Mean tumor size (mm): 34.5 (30-39).

Mean operating time (min.): 97.5 (45-150); Mean estimated blood loss (mL): 75 (50-100).

Mean postop.hospital stay (days): 8 (4-12); Tumor histology: myelolipoma and schwannoma.

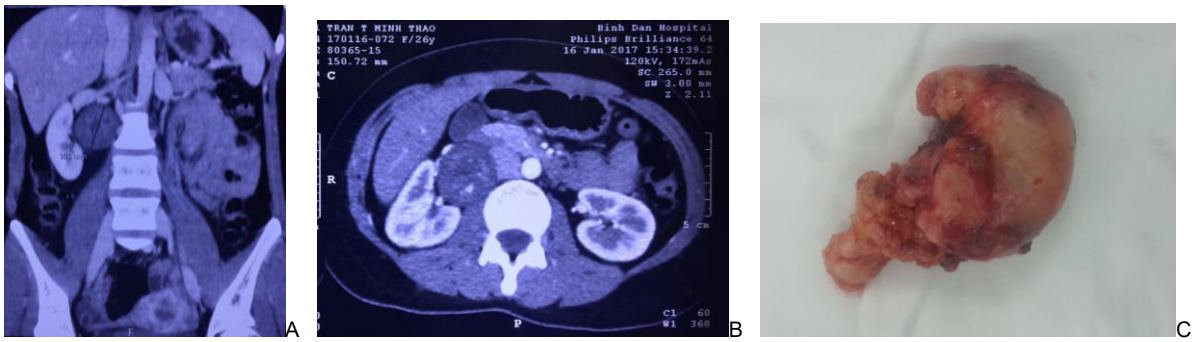


Figure 15. *Schwannoma on right adrenal. A.B. MSCT with contrast. C. Specimen*

3 cases of nephroureterectomy for upper tract transitional cell carcinoma (Fig.16)

Gender: 2 males, 1 female; Mean age: 54 (47-55); ASA score 2: 3 cases.

Right side: 2 cases, Left side: 1 case.

Mean operating time (min.): 240 (210-270); Mean estimated blood loss (mL): 800 (400-900); Mean postop.hospital stay (days): 6 (5-7).

Tumor histology: upper tract transitional cell carcinoma in 3 cases.

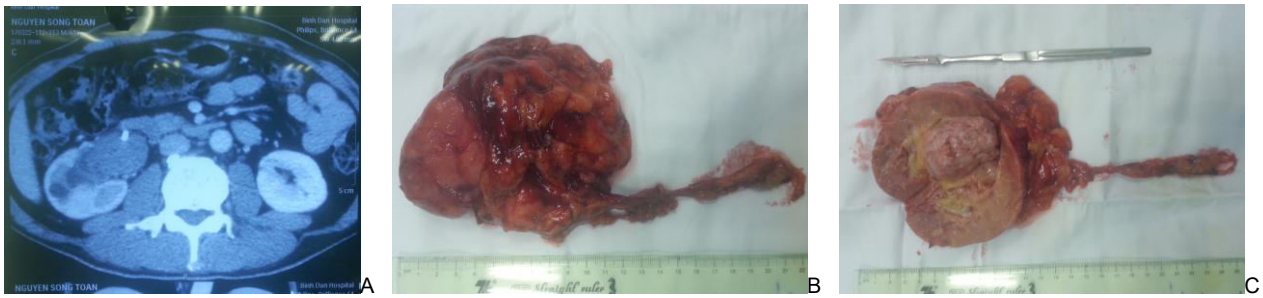
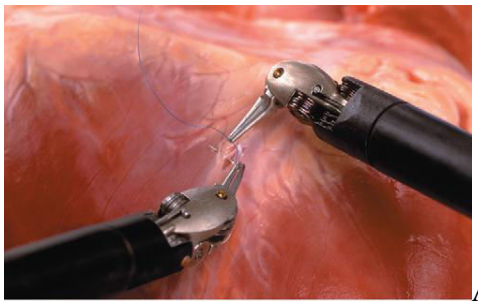


Fig 16. *Transitional cell carcinoma of right renal pelvis A. MSCT with contrast. B.C. Specimen*

DISCUSSION

The advantages of the da Vinci™ robot system[7]

Surgeon's side: the robot surgical system enhances the dexterity with greater surgical precision, increased range of motion, tremor reduction, motion scaling, improved ergonomics and comfort for the surgeon. Its stable magnified, 3D view is controlled by the surgeon. The surgeon manipulates both the camera and two to three instrumented arms. The Endowrist™ technology has 7 degrees of freedom with which to operate the instruments (Fig.7). The instruments' movements are directed by the surgeon's fingers and wrists, making it feel far closer to open rather than standard laparoscopy. Thanks to these advantages, the da Vinci™ system allows the standard laparoscopy naïve surgeons to study to perform upfront the most sophisticated procedures such as radical prostatectomy, pyeloplasty,…


A

B

Fig. 17. *A. Endowrist™ technology. B. The surgeon's fingers manipulating the joysticks*[7]

Patients' side: reduction in blood loss, transfusion rate, hospitalization time, catheterization time, and perioperative complications and the potential for improved oncologic outcomes, continence rates, and potency.

Other advantages: smaller incisions, less pain, less hospitalization time, shorter convalescence, and less time to get back to work. Reduction in blood loss and transfusion rate has been shown consistently in robot-assited radical prostatectomy[7].

Which urological procedures are in priority of being performed with robotic assistance?

According to Schachter[7]:

- Prostatectomy (RALP)[2,8]
- Pyeloplasty[3]
- Radical cystectomy (RALC)[9]
- Partial nephrectomy(RAPN), radical nephrectomy[1]
- Sacrocolpopexy[4]
- Vasovasostomy
- Pediatric urologic procedures (nephrectomy, partial nephrectomy, pyeloplasty, antireflux)
- Adrenalectomy[6]
- Ureterolysis, ureteroureterostomy[5]

The lower tracts procedures such as RALP, RALC, sacrocolpopexy,… reveals the consistent benefits of minimally invasive surgery, while those of upper tracts procedures remains more or less controversial. The ports placement in upper tracts procedures (e.g. RALP) is more constant in comparison to those of upper tracts procedures (e.g. RAPN). In lower tract procedures, the docking is generally easier than in renal/upper tract procedures (fighting of the robotic arms). In 2 of the 6 cases of partial nephrectomy, we couldn't use the 4th arm due to fighting of the 3rd arm and the 4th arm. The 4th arm is of utmost importance when connected to the ProGrasp™.

During one specific procedure, the da Vinci™ robot system makes it easier to perform specified techniques that require the flexibility of movements of surgical instruments. For example, in radical prostatectomy, it is easier to perform bladder neck-urethra anastomosis, more rapid and easier to perform the Rocco's stitches under the very clear and bright 3D vision. In the end-to-end anastomosis, when using the barbed suture (V-loc® or Stratafix®), the suturing is more rapid and more water-tight because the thread has a self-holding mechanism.

Credentialing

According to the authors[7], the surgeons who will use the robot need to be credentialed. A good credentialing system involves (1) board certification or board eligibility in the surgeon's appropriate surgicalboard, (2) privileges for both the open and laparoscopic surgery to be performed robotically, (3) completion of a specified robotic training course, (4) performance of robotic surgery in an animal model, (5) observation of expertly performed robotic surgery, (6) acting as bedside assistant for robotic surgery, (7) observation by a proctor of initial robotic surgical cases, and (8) ongoing monitoring of surgical outcomes of robotic surgical cases.

Our robot surgeons have been trained in Intuitive™ robot training centers such as Severance hospital, Asan hospital, Seoul, South Korea. The trainees obtained the Certificate of da Vinci™ system Training as a console surgeon after undergoing training on the models and on experimental animals and attending 6 robotic surgeries performed by experienced Korean robot surgeons. Three urologic robotic surgeons when coming back from abroad performed five initial robotic cases under the supervision of a foreigner robot proctor: one pyeloplasty, two radical prostatectomies, one partial nephrectomy, one sacrocolpopexy During these robot assisted procedures, the surgeon and the

proctor have replaced with each other the roles of the console surgeon and the bed assistant.

Remarks on this initial series

The two most common procedures in this series were RALP for prostate cancer and RAPN for small renal masses. The biggest number of cases were radical prostatectomy, in which the robot surgical system presents more clearly its superiority over standard laparoscopy and open surgery. In the RALP sub-groupe, four cases of capsule invasive tumors and seminal vesicals invasive prostate cancers (two cases of T3aNoMo and two cases of T3bNoMo) were successfully performed robotically without conversion to open surgery. In standard laparoscopy, we feared the capsule invasive tumors due to high conversion rate caused by the "stone-hard" cancerous infiltration. When using the robot for malignant diseases, we find out that this system helps us not only in the more extended and faster lymphadenectomy, but it also makes the radical extirpation procedures more amenable without conversion to open surgery.

Patient recruitment

For patient recruitment, we counsel the patients about the benefits of robotic surgery over standard laparoscopy (difficult) open surgery (easier). The combination of (1) media's health education (2) the surgeon's reputation (3) the dedication of the counsellor could convince the patient and his family to accept the high-cost robot option when surgery is called for. The question is "recruit the patients wishing and capable to afford robotic surgery or recruit only the patients with procedures recommended for robotic surgery?". If we recruit all the patients willing to be treated with robot regardless of the type of procedures, there is a risk of decreased cost effectiveness, if we recruit only the patients with procedures in which robot use is strongly recommended, many of them couldn't afford the robot cost, currently not re-imbursed by the national health insurance, and the numbers of robotic procedures that could be performed would be very limited, not enough to maintain the running of the system.

CONCLUSION

Robot-assisted surgery, with many advantages over standard laparoscopic/ open surgery thanks to technological innovations (the 3D-HD vision, the robotic arms with Endowrist™ function, comfortable console table,…) has helped the urologists to perform the sophisticated procedures in urooncology with shorter learning curves. Our initial series of 35 robot-assisted urooncological procedures has achieved encouraging outcomes. More cases are to be performed in the future.

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TRIDIMENSIONAL TITANIUM-PRINTED PATIENT-SPECIFIC PROSTHESIS FOR MANDIBULE RECONSTRUCTION

TRUONG X. BUI[1], KHOI A. NGUYEN[1], VU T. NGUYEN[2]

Today, titanium implants are preferred by many surgeons because of their optimal features. Tridimensional (3D) laser printing techniques allow us to fabricate more complex implants structures. We present 4 cases of madibule reconstruction by means of a 3D titanium printed patient-specific prosthesis after extensive resection. The use of an intraoperative template to precisely set resection margins, the novel prosthetic design as well as a new and safer mandibule fixation system may offer some advantages over the conventional reconstructive plates systems.

Threedimensional printed prosthesis of the mandible is a viable alternative to segmental mandibulectomy.

INTRODUCTION

In recent years, threedimensional printing technology has become the focus of attention in many fields of medicine. This technique has been utilized for many situations, such as customized operative instruments. Although some cases with 3D printed prosthesis, such as tailormade hip replacement, have been reported via mass media, only a few cases have been published by medical journals to date1,4.

Free tissue transfer has become a standard option for reconstructing major segmental defects of mandible. This option generally provides excellent results but can be associated with significant patient morbidity. With a short bone gap, we can choose among the techniques such as nonvascularized bone grafting, metal plates, or regional flaps.

Patient-specific prothesis is an alternative for the conventional metal plates to reduce surgical complications and to maximize functional outcomes.

PATIENTS AND METHODS

A case series of surgical patient with mandible defect smaller than 6cm at Surgery Department 5 of Oncology Hospital HCMC 2017.

All patients were diagnosed by madibular lesion biopsy. The prosthesis, which is mirror image of the contralateral intact madibular, was custom made (Computational Modelling) by an Electron Beam Melting 3D printer (CSIRO High Performance Metals Technologies, Australia) based on helical CT DICOM data. The prosthesis is made from Ti6Al4V.

A saw-guide polyactic acid (PLA), from 3D printer in Vietnam, was applied to patient madibular for an accurate resection. After ablative surgery, the prosthesis was engaged to the remaining mandibular.

All patients were followed up 1 month, 3 months, and 6 months postoperatively. We evaluated the status of prosthesis: (1) local infection, (2) implant exposure, (3) stability. All patients were evaluated dental occlusion and masticatory function. A panel of three surgeons assessed the cosmetic outcomes.

RESULTS

There were 2 men and 2 women, the youngest is 32 years and the oldest is 59 years. The mean operative time was 98 min (range, 86-125).

[1] PhD, MD, Surgery Department 5 of Oncology Hospital HCMC

[2] PhD, Senior Scientist, Computational Modelling, High Performance Metals Industries, CSIRO Manufacturing

Case No.	Sex	Age	Diagnosis	Site of defect	Size of defect (mm)
1	Male	32	Amenoblastoma	Lateral	35
2	Male	59	Mucoepidermoid carcinoma	Lateral	42
3	Male	46	Amenoblastoma	Lateral	60
4	Female	40	Fibrous dysplasia	Lateral	44

We have two cases with intraoral exposure of prosthesis at 2 months postoperatively, fistulas size about 1cm. We have used the buccinator myomucosal flap to repair these fistula. Stability of prosthesis is perfect for all patients. Deltal occlusion and masticatory fuction were recovered at 1 month postoperatively. The cosmetic outcomes are excellent in 100% of our patients.

DISCUSSION

Mandible reconstruction can be accomplished by a variety of means, including nonvascularized bone grafts, metal plates, pedicled flaps, and free flaps. Nonvascularized grafts can be used for a short bone gap (<3cm) in a setting of benign disease. This is not a standard application.

Pedicled flaps include the trapezius and pectoralis osteomyocutaneous flaps. The greatest limitation of regional flaps is that they do not provide enough tissue in the proper configuration to be useful. The bone available with the pectoralis major muscle (rib) and the trapezius (spine of the scapula) is limited compared to free-flap alternatives[2].

Metal reconstruction plates offer advantages of decreased operating time and avoidance of a bone graft donor site. They have important disadvantages such as: risk of exposure or infection; risk of plate fracture; preclusion of dental reconstruction; and a thin shape that does not provide adequate bulk for reconstruction[2]. We hope to have a patient-specific prosthesis so that we can solve problems of the conventional plates.

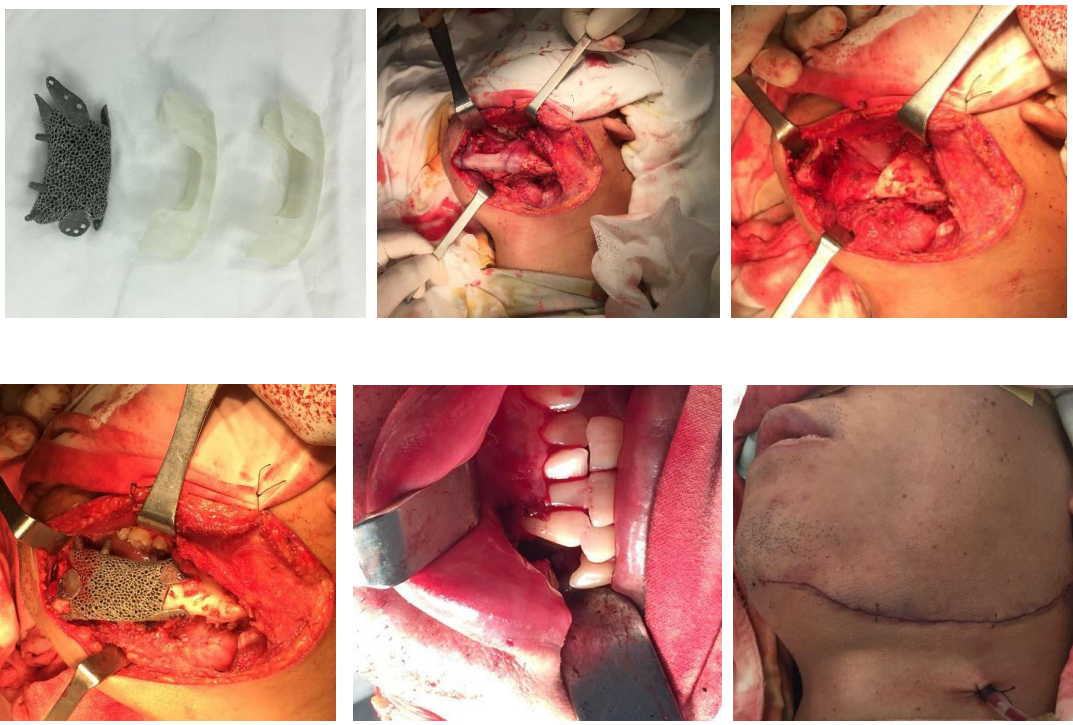

Figure 1. *Mandibular reconstruction with tridimensional titanium-printed patient-specific prosthesis*

Our patient-specific prosthesis is one of the first mandibular implants all over the world. At St. Vincent's Hospital Melbourne, a similar prosthesis was printed to reconstruct the defect after total calcanectomy for a calcaneal chondrosarcoma. Five months after surgery, the patient was free of pain without medication, and could walk unsupported on bare feet[4]. Salamanca University Hospital,

Salamanca, Spain, there was a case of sternocostal reconstruction by means of a 3D titaniumprinted custom-made prosthesis after extensive resection of a chest wall sarcoma. The use of an intraoperative template to precisely set resection margins, the novel prosthetic design as well as a new and safer rib fixation system may offer some advantages over other custommade reconstructive techniques[1].

With the growing availability of three-dimensional radiographic computer modeling, surgeons can preoperatively analyze bony and soft tissue defects through virtual manipulation. This can even be done for existing defects, but also prospectively to forecast a defect that will result from an ablative procedure. With this technology comes the ability to fabricate *patient-specific implants* (PSis). Using the patient's native contralateral anatomy or gender- and age-specific norms, implants can be constructed to replace tissue loss in multiple dimensions[3].

Metallic devices can be composed of a single metal or an alloy of several metals. Alloys are developed to improve qualities of the original metal by adding other metals with characteristics that improve biocompatibility or mechanical attributes. The principal metals used in facial implants are titanium, stainless steel, and tantalum. Chromium, aluminum, cobalt copper, nickel, and tungsten are included in alloys. The material must be designed to meet the functional requirements of the dental or maxillofacial implant. A relatively brittle metal, such as stainless steel, can function well initially but with longterm use can fail because of fatigue. All metals corrode when exposed to living tissue; the gradual result is failure of many metal implants. Stainless steel, an alloy of iron, chromium, nickel, molybdenum, and manganese, resists corrosion well. It can, however, undergo gradual plastic deformation[3].

Titanium and its alloys are among the most biocompatible metallic implants used today. Titanium is lightweight and corrosion resistant and has high tissue acceptance[3]. Our madibular prosthesis were light-weight and its strength was thought enough. Small round holes of 3mm diameter were designed (mesh structure) to promote tissue integration.

The prosthesis was designed from the patient-specific three-dimensional radiographic computer modeling. So we can decrease the implant engage time. The hard prosthesis can not be reshaped during operative procedure, a saw-guide polyactic acid has been utilized for an accurate resection.

CONCLUSION

This is only a first step towards a large study, the initial results were satisfactory. Three dimensional printed prosthesis of the mandible is a viable alternative to segmental mandibulectomy.

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A STUDY OF MALNUTRITION STATUS AND NUTRITIONAL PROBLEMS OF PATIENTS WITH CANCER TREATED IN THE HO CHI MINH CITY ONCOLOGY HOSPITAL

TRAN THI ANH TUONG[1]

ABSTRACT

A prospective study was performed on 480 patients with cancer treated with a multidisciplinary therapy in the HCM City Oncology hospital. Their tumors were located on nasopharynx, lung, esophagus, stomach, colon, cervix, breast, ovary and lymph node system. At the administration, the incidence of malnutrition was 34.8%, the incidence of overweight and obesity patients were 12.9%. Patients with gastric and esophageal cancer were mostly malnourished (70%). The incidence of weight loss before administration was up to 65.3%, loss of weight more than 5% was about 36.8%. After treatment, the incidence of weight loss was not improved about 61.2%, half of them were patients who had the history of loss of weight before. The rate of loss of weight was different among cancer therapies, in which radiotherapy and concurrent chemoradiotherapy accounted the majority of weight loss (68-78%). Patients at any age had the same risks of weight loss. The patients's energy dietary intake over 24 hour was average 1300kcal (460-1900kcal), accounting 77,4% their energy requirement of 1675 kcal (1239-2138kcal). There was only 5.6% patients took enough food and 1/3 patients took less than 75% energy requirement. However, only 12,6% of malnourished patients were dietary consulted, 19% of patients were tube feeded, 9% of them were supplied with parenteral nutrition. Half of patients were still malnourished eventhough tube feeding was given. Other problems related malnutrition could be: low income (72%), rural resistance (83%), no care giver (8%), uncontrolled pain (36%), insomnia(34%), loss of appetite(33%), and nausea(30%).There were 31 patients delayed treatment, 29 patients stopped treating, and 18 patients had severe pneumonitis.

INTRODUCTION

Patients with cancer, geriatric diseases and critical illness have the highest risks of malnutrition, accouting for 30-80%. [2]The incidence of malnutrition depends on study methods, hospitals, countries, cancer stages, tumor locations. Also, it is always changed during cancer treatment. About 2/3 of patients with cancer became malnourished and 1/5 of them died of cachexia[2]. In the HCM City Oncology Hospital, there were some surveys studying the malnutrition incidence of patients of head and neck cancer, gastrointestinal cancer by BMI, Albumin, SGA. The incidence of malnutrition ranged from 16 to 67%. Patients with colon cancer and hypopharyngeal cancer had the highest incidence of malnutrition[9,10]. In 2015, the European Society of Clinical Nutrition and Metabolism (ESPEN) introduced the new definition of clinical malnutrition including BMI and the percentage of weight loss. Malnourished patients are people who have BMI<18.5 or lose more than 10% their usual weight. They are also malnourished if they lose more than 5% their usual weight and their BMI less than 20 (<70 years old) or their BMI less than 22 (>70 years old). In my hospital, we have not used this new concept in studies relating clinical nutrition yet. Moreover, we wanted to know the changing of weight during treatment, the incidence of cachexia, and the actual problems affecting malnutrition in hospital. That was the reasons why we performed this study. The objectives of this study were:

- To estimate the incidence of malnutrition of top ten common cancers before and after treatment.
- To calculate the incidence of the cancer cachexia.
- To evaluate the risk factors of clinical malnutrition in the HCM City Oncology hospital

METHOD

Study population

Patients who have cancer of nasopharynx, lung, esophagus, larynx, stomach, colon, cervix, breast, ovary, and lymp node system were included in study.

[1] MD and Nutritional Support Team in the HCM Oncology Hospital

They have been treated in the HCM Oncology hospital from Jannuary 1st to May 31th 2017. There were at least 30 cases of each cancer.

Patients were excluded when they refused to treat cancer.

Study method

This was a prospective study. All patients were measured height, weight at beginning, during and finishing treatment. Also, they were asked questions relating 24 hour - dietary energy, symptoms and barriers causing malnutrition.

Following criteria of European Society of Clinical nutrition and Metabolism, malnutrition was defined as:

- BMI<18.5.
- Loss of weight >10% usual weight.
- Loss of weight >5% usual weight and BMI<20 at the age <70 years old, or BMI <22 at the age > 70 years old.

RESULT

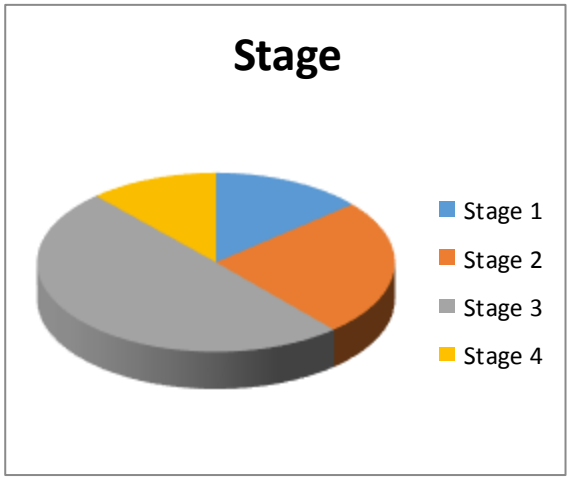
Social characteristics of study patients

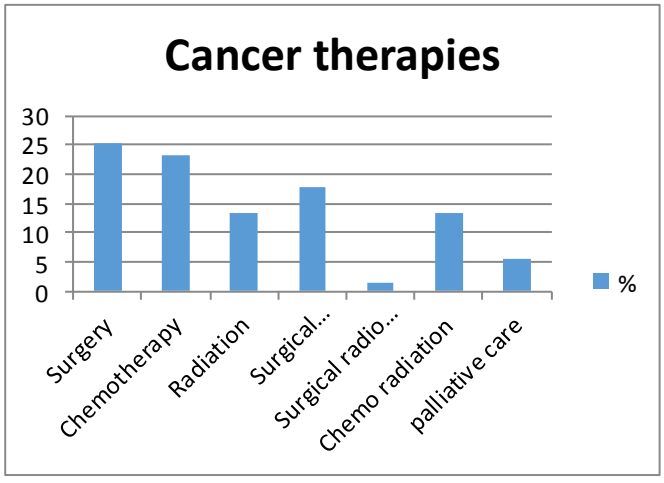
Medial age: 54.3 (18-99).

Characteristic	Number	%
Sex		
Male	280	58,3
Female	200	41,7
Residency		
Urban	400	83.3
City	80	16.7
Education		
Illiteracy	**2**	**0.4**
Primary school	**162**	**33.8**
Secondary school	161	33.5
High school	116	24.2
Tertiary	39	8.1
Financial status		
No income	**139**	**29**
<5 million	**210**	**43.8**
5-<10 million	108	22.5
≥10 million	23	4.8

Pathology

	Cases	%		Cases	%
Cervical cancer	50	10.4	Esophageal cancer	**54**	11.2
Breast cancer	70	**14.6**	Gastric cancer	**30**	6.2
Ovarial cancer	42	8.8	Colon cancer	**30**	6.2
Lung cancer	53	11	Laryngeal cancer	**50**	10.4
Lymphoma	51	10.6	Nasopharyngeal cancer	**50**	10.4





Malnutrition index

	Before cancer treatment	After cancer treatment
Malnutrition	167/480 cases (34.8%)	182/480 cases (37.9%)
Loss of weight	318/476 cases (66.8%)	294/480 cases (61.2%)
Loss >5% usual weight	175/476 cases (36.8%)	172/480 cases (35.8%)

More than 50% patients kept loosing weight during treatment.

Malnutrition and cancer

	Number	%
Cervical cancer	18	38
Breast cancer	15	21.4
Ovarian cancer	11	26.1
Lung cancer	25	**47.1**
Lymphoma	14	27.4
Esophageal cancer	42	**79.2**
Gastric cancer	22	**73.3**
Colon cancer	2	6.7
Laryngeal cancer	14	28
Nasopharyngeal cancer	8	16
Total	**167**	**34.8**

The highest prevalences of malnutrition belonged to esophageal, gastric and lung cancer.

Weight loss and therapies

	Number	%
Surgery	71	58.1
Chemotherapy	63	56.2
Radiation	**44**	**68.7**
Surgical chemotherapy	46	54.1
Surgical radiotherapy	3	42.9
Radio chemotherapy	**49**	**76.6**
Palliative care	**18**	**69.2**

Patients with concurrent chemo radiation or radiation lost weight most.

Weight loss and age

Age groups	Number	%
Teenager (<35 years old)	19	57.6
Middle age (31-60 years old)	187	61.9
Old age (>60 years old)	88	60.7

Loss of weight may happen at any age during cancer treatment.

Energy requirement and 24h diet recall

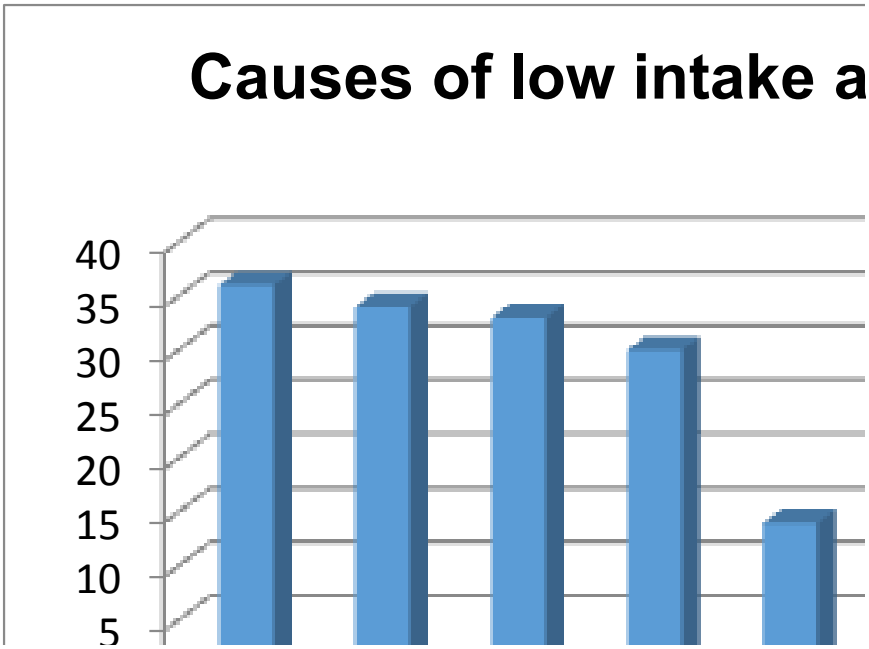
Energy requirement (30kcal/kg/day): 1675 kcal (139-2138 kcal).

24h dietary recall: 1297 kcal (460-1900 kcal).

Energy intake	Number	%
100% requirement	27	5.6
75,1-99,9 %	235	49
50,1-75%	**168**	**35**
<50%	**19**	**4**

40% patients can not take enough energy requirements per day.

Causes of low intake at the hospital



Malnutrition and outcome

	Number	%
Delayed treatment	31	6.5
Stopped treatment	29	6
Pneumonitis, infection	18	3.7
Blood infusion	29	16

Malnutrition and nutrition intervention

	Number	%
Dietary counselling	21	12.6
Tube feeding	91	19
Parenteral nutrition	43	9

DISCUSSION

Ther were 480 patients with the top ten of common cancer including nasopharynx, lung, esophagus, stomach, colon, cervix, breast, ovary and lymph node system. This is the study with the largest number of cases in the HCMC Oncology hospital. And, it is the only prospective study recording the weight changes during cancer treatment. At the administration, the incidence of malnutrition was 34.8%. This incidence may be higher if the cases of breast cancer patients in study were not much more than other cancer patients. Also, it was different from malnutrition rate of the prior nutrition studies in my hospital. It was ranged from 16% to 65.2%. [9,10]The reasons could be: different nutrition assessment tools, different cancer. In this study, the malnutrition rate was different among locations of tumor. The lowest malnutrition rate was colon cancer and the highest rate was esophageal cancer. Patients with gastric and lung cancer had the higher risk of malnutrition. If we have just used BMI to evaluate malnutrition status, the incidence of patients having BMI lower than 18.5 was 19%. Clinically, eventhough patient had BMI higher than 18.5, they still had nutrition risk if their weight changes were dramatical. So, weight loss is the important index that ESPEN included in definition of malnutrition. [7]The number of patients with a significant weight loss at administration was 175 cases (36.8%). Belongs to ESPEN's definition, malnutrition rate became to 34.8%.

After treatment, the malnutrition rate was high, too. It came to 37.9%. The incidence of weight loss was still high 35.8%, half of them were patients who had the history of loss of weight before. Some causes of high malnutrion rate could be urban residence (80%), low education (40%), low - income class (70%), advanced stage of cancer (60%). Patients at any age had the same risks of weight loss. In another study, age did not affect to weight loss. [3]In my hospital, most patients were indicated a multidisciplinary approach. Among cancer therapies, radiation and concurrent chemoradiation therapy caused severe weight loss. 42% to 76.6% patients kept loosing weight during and after treatment.

Unfortunatedly, there were 38% patients were anaemia before treatment. It was increasing to 72.5%. 16% of them have been blood transfused.

When we performed 24h dietary recall, there were only 2/3 patients taking more than 75% energy requirement, 5.6% patients got enough energy per day. The average energy intake was 1300 kcal, approaching to 77.4% energy requirement. However, only 12.6% of malnourished patients were dietary consulted, 19% of patients were tube feeded, 9% of them were supplied with parenteral nutrition. There were many barriers in nutrition intervention including uncontrolled pain (36%), insomnia (34%), anorexia (33%), and nausea (30%) et etc... 70% patients had to use free meals from charity activities. So, sources of food were not stable. Moreover, the composition of meal was not suitable for hospitalized patient such as lack of protein, higher sodium, less fiber, lack of essential fatty acid. Eventhough patients with tube feeding did not intake enough energy just about 74% target goal. There were 55% patients still loosing weight with tube feeding.

Some treatment troubles relating malnutrition were 6.5% delayed treatment, 6% stopped treatment, 3.7% pneumonitis and infection. If the patients were fed better, we hope that these problems were limited.

CONCLUSION

A prospective study was performed to evaluate malnutrition status before and after cancer treatment. With a large number of cases, the result of this study was remarkable. Patients with cancer had the incidence of malnutrition about 35%. Esophagus, gastric and lung cancer had the most malnutrition rate. Loss of weight was usually considered to assess nitrition status. Patients with weight loss at administration kept developing during treatment. And, patients with tube feeding were still under fed. Among cancer therapies, radiation and chemoradiation therapy caused weight loss most. To improve nutrition status of patients, we think that nutrition consulting should be indicated at the first days of hospitalization for patients who had BMI lower than 18.5 and lost weight more than 5% usual weight. And, patients with tube feeding must to be fed properly.

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TREATMENT OF FIBROADENOMA BY ULTRASOUND-GUIDED VACUUM ASSISTED BREAST BIOPSY AT HO CHI MINH CITY ONCOLOGY HOSPITAL

LE HONG CUC[1], TRAN VIET THE PHUONG[2], PHAM THIEN HUONG[3], PHAM HOANG TU[4]

ABSTRACT

Introduction: *VABB is effective for complete removal of benign lesion of the breast such as fibroadenoma.*

Method: *breast lesions which are diagnosed fibroadenoma by ultrasound and less than 3cm are removed by ultrasound-guided VABB and local anesthesia.*

Result: *20 patients with 39 lesions are removed with ultrasound guided VABB. All histology turns out benign with 22 fibroadenomas. Mean age is 37.5 (11-54), mean size is 16.7mm (9.5-30mm). 8 cases with one tumor (40%), 6 cases with 2 tumors (30%), 5 cases with 3 tumors (25%) and 1 case with 4 tumors (5%). There is no severe complication, 5 cases with skin echymosis and 1 case with hematoma. None of the patients feels pain.*

Conclusion: *VABB is an effective for diagnosis and treatment of benign breast lesion, including fibroadenoma with small size.*

INTRODUCTION

Fibroadenoma is the most common benign tumor of the breast. Treatment of this type of tumor is either follow up or removal. Follow up is often for small tumors, mupltiple tumors, young patients, or patients who do not like surgery. Conventional treatment for tumor removal is open surgery. This type of technique is relatively simple, with local anesthesia (if tumor is not big). However, this technique has disadvantages such as leaving scars, is an invasive method, and post-op care is necessary.

Vacuum assisted breast biopsy (VABB) has been performed worldwide since the 1990'. This technique uses bigger needle (7G, 8G, 11G) and could biopsy or completely remove small benign tumor (less than 3cm). Therefore, this is a method for biopsy of breast lesions and also for treatment of benign breast lesions. This technique has been approved by FDA (USA) and NICE (UK) for complete removal of fibroadenoma.

In our knowledge, VABB has not been performed and reported in Vietnam until 2017. In this article, we report our series of breast tumors diagnosed fibroadenomas by ultraound and treated with VABB at Ho Chi Minh City Oncology Hospital in 2017, which is the first reported series in Vietnam.

METHOD

Patients who have breast tumors diagnosed fibroadenoma on ultrasound and less than 3cm are recruited. Patients will have consultation about options of follow up, open surgery or tumor removal with VABB, pros and cons of each option.

When the patient decides to have VABB, her breasts are examined again with ultrasound by the radiologist of the team. The character of the tumors, number and the size of the tumors are recorded. Patients are also informed about the number of the tumor removed. If there are multiple tumors, we decide to remove 2 to 3 tumors, those smaller than 10mm will be followed up. The number of the removed tumor is also decided by the patient.

The procedure is performed at the Radiology department. Before the procedure, breast ultrasound will be done to decide the entry of the probe. Local anesthesia is with 20ml of Lidocain 1% (with Adrenalin) by 25G needle and then 18G needle. Lidocain is injected behind and above the tumor.

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[3] Department of Breast Surgery-Ho Chi Minh City Oncology Hospital
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The purpose of Lidocain injection is local anesthesia, hemostasis and to prepare the route for the probe.

The procedure is performed by radiologists or breast surgeons who have been trained with VABB. A small orifice will be made by a 11 blade to insert the probe. The size of the probe will be depended on the size of the tumor and the if the tumor is close to the skin or not. The probe is inserted behind the tumor, at 6:00 position. When the position of the probe is accurate, the Legacy machine (Mammotome-USA) is activated and will cut and remove the tumor. The process of removal of the tumor is visualized under ultrasound until the tumor is removed completely and the probe is withdrawn afterward.

A nurse will compress the breast in 5 minutes for hemostasis and the orifice is tapped. Patient stays at the hospital in 30 minutes and will be instructed to remove the tap the day after. Patient will take pain killers if painful but antibiotics is not prescribed. Patient comes back in 10 days for histology result, clinical and ultrasound examination.

Pain is evaluated on the scale of 1-10. Evaluation is taken before the procedure, after the procedure and 10 days after the procedure.

Figure 1. *VABB Mammotome-Legacy machine*

Figure 2. *Performing VABB*

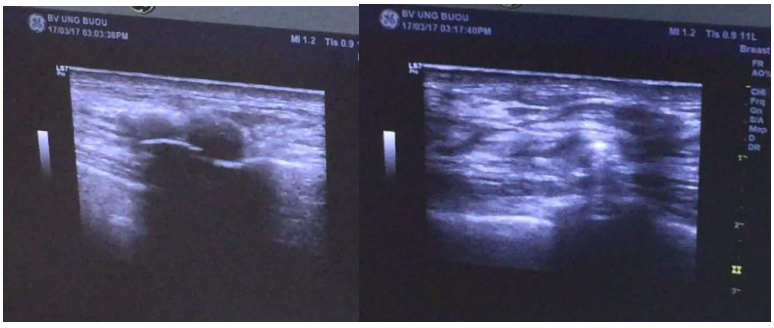

Figure 3. *Complete removal of Fibroadenoma with VABB*

RESULT

There are 20 patients (39 tumors) diagnosed fibroadenoma on ultrasound and treated with VABB. Mean age is 37.5 (11-54). Mean size: 16.7mm (9.5-30mm). There are 8 patients with 1 tumor (40%), 6 patients with 2 tumors (30%), 5 patients with 3 tumors (25%), and one patient with 4 tumors (5%).

Pathology results of 39 tumors are 22 fibroadenomas, other pathology results are borderline phyllodes tumor, fibrocystic changes, intraductal papilloma and granulloma mastitis (Table 1). Four patients diagnosed fibroadenoma turn out benign lesion (not fibroadenoma), 16 cases have at least one fibroadenoma.

Pathology	Number
Fibroadenoma	22
Borderline phyllodes tumor	1
Fibrocystic changes	10
Intraductal papilloma	4
Granuloma mastitis	2
Total	**39**

Table 1. *Pathology results*

Complications are mild, including 5 cases with ecchymose of the skin of the breast, one case with hematoma and needs puncture. There are no infection, bleeding or chest wall injury.

All the patients do not have pain in the duration of the procedure, after the procedure and 1 week after the procedure.

Breast ultrasound shows that there is no residue after the procedure and 10 days afterwards.

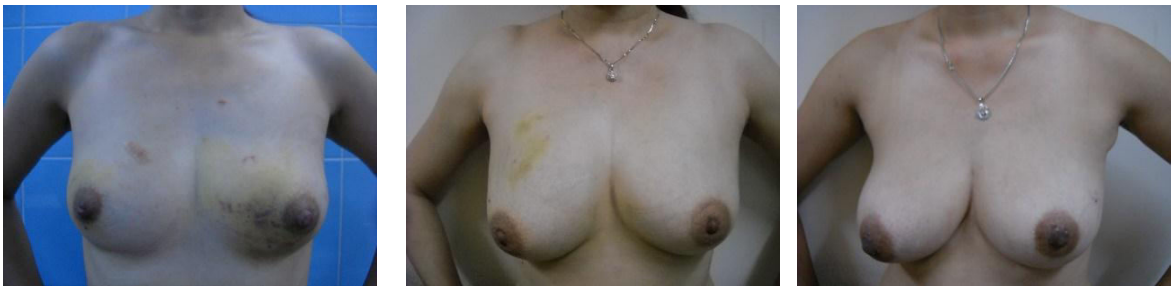

Figure 4. *Ecchymose* *Mild ecchymose* *No ecchymose*

DISCUSSION

Fibroadenoma is the most common tumor of the breast. For a long time ago, treatment for this kind of tumor are follow up or open surgery. Follow up are for young patients, small tumor (<1cm) and multiple lumps. However, some patients worry about the tumor and want to have the tumors removed for histology and VABB will give the patients a good option because it is less painful, does not leave a big scar and multiple lumps could be removed in one time.

VABB has been performing since 1995 and becoming an efficient device for biopsy of breast lesions. VABB is useful for lesions small than 5mm which are not applicable for core biopsy. The probes of VABB are bigger enough to provide large sample for histology. Not only for biopsy, VABB has been aproved by FDA and NICE for treatment of benign breast lesions like fibroadenoma. In these situations, VABB provides patients an alternative of open surgery without big scar. VABB could also remove multiple tumors in one time. Povoski report a case in which VABB removes 14 fibroadenoma of a 21 year old patient.

In the report of Karol with 196 cases diagnosed fibroadenoma by ultrasound, only 157 cases (80.1%) are fibroadenoma on histology, and 2 cases are invasive carcinoma. In the series of Thurley with 134 cases diagnosed benign in ultrasound, only 81 (60.4%) are fibroadenoma on histology. In our series, 75% are fibroadenoma pathologically. The remaining cases are benign except one borderline phyllodes. In this case, patient rejects the option of wide excision and decides to have follow up.

In our series, we do not use VABB for tumor bigger than 30mm (mean size is 16.7mm). When the tumor is too big, the vacuum force and the aperture of the probe could not completely remove the tumor.

In the series of Karol, the mean size of the tumor is 13.53 mm. Two big tumors (50mm and 60mm) could not be removed completely.

Like Lui, we use the probe 11 for lesions smaller than 1cm và 8 for lesions bigger than 1cm. The choice of the size of the probe also depends on the position of the tumor and skin, if the tumor is very close to the skin, probe 8 could not be used to protect the skin.

Similar the series of Sperber with 52 cases, we do not have any patient with pain in the procedure or afterwards.

VABB seldom has complication and often mild. Two patients of Sperber has bleeding and resolve with compress. In 2477 cases of Lee, only 3 has bleeding and compression could resolve the problem. Only 19% of patients of Thurley has echymoses. We have 5 cases with mild ecchymoses and only one case needs withdrawal for hematoma.

VABB has some disadvantages. In Vietnam, higher cost of VABB compared to open surgery is an obstacle. This is a sophisticated technique and need learning curve, radiologists and breast surgeons need to master ultrasound guided intervention technique. Bigger tumors is relative contraindicative of this procedure.

CONCLUSION

VABB is an efficient method for diagnosis and treatment of breast benign lesions, including small fibroadenoma. This is a promising and potential option for treating of fibroadenoma in Vietnam.

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INITIAL EVALUATION OF MMR STATUS TESTING IN THE TREATMENT OF STAGE II COLON CARCINOMA

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***Background**: Prior reports have indicated that patients with colon cancer who demonstrate high-level micro-satellite instability (MSI-H) or defective DNA mismatch repair (dMMR) have improved survival and receive no benefit from fluorouracil (FU)-based adjuvant therapy compared with patients who have microsatellite-stable or proficient mismatch repair (pMMR) tumors. We examined MMR status as a predictor of adjuvant therapy benefit in patients with stages II colorectal cancer.*

***Methods**: In this cross-sectional with logitudinal follow-up study, immunohistochemistry for MMR proteins were performed on 46 patients with stage II colon carcinoma (from Apr-Sept 2017). The MMR status and its impact on clinical decision were investigated.*

***Results**: The defect MMR rate is 30,4%, in which loss of manifestation of MLH1-PMS2 is 14,3%, MSH2-MSH6: 6,5% (Lynch syndrome). 60,9% of patients had choosen the adjuvant treatment with the aid of MMR results.*

***Conclusion**: MMR status assessment by IHC staining is feasible for patients with stage II colon carcinoma. MMR status contributes to the treatment decision with its prognosis and predictive values.*

***Key words**: colon cancer, mismatch repair, microsatellite instability, adjuvant chemotherapy.*

INTRODUCTION

Colon cancer is one of the most common malignancies on over the world and also in Vietnam. According to GLOBOCAN 2012, colon cancer is third most common cancer in male (10%) and second most common cancer in female (9,2%). In Ha Noi Cancer Registry from 2001-2004, colon cancer is in fourth position of most common cancers with the ASR 13.9/100,000 in male and 10.1/100,000 in female. According to Ho Chi Minh City Population Cancer Registry in the period of 2007-2011, colon cancer is the third most common cancer in male with ASR 16.2/100,000; fourth in female with ASR 8.8/100,000.

Surgery remains a curatively radical treatment of colon cancer. However, more than 50% of stage II colon cancer have postoperative reccurrence because of micrometastasis. Many clinical trials have demonstrated the role of adjuvant chemotherapy in stage III colon cancer, which prolonged disease free survival (DFS) and overall survival (OS). Adjuvant chemotherapy has become standard of care for stage III colon cancer since 1990. In spite of that fact, the benefits of adjuvant chemotherapy in stage II colon cancer still remain controversial. Although adjuvant chemotherapy is indicated routinely for high risk stage II colon cancer (less than 13 lymph nodes evaluated, stage T4, tumor penetration, neural or vascular invasion, poor differentiated histology), still no data has been identified in choosing the group of stage II colon cancer patients who are beneficial from adjuvant chemotherapy. Actually, data from U.S SEER/Medicare database showed that adjuvant chemotherapy did not improve OS for stage II colon cancer patients regardless of high risk factors.

Recent studies have revealed the potential use of molecular and biochemical markers in CRC to predict outcome and response to chemotherapy.

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The CRC carcinogenesis is usually a result of mutations in the adenomatous polyposis coli (APC) gene which are characterized by chromosomal instability (CIN). However, 10–15% of all sporadic colorectal cancers arise via the microsatellite instability pathway (MSI). Tumors arising from the two separate pathways CIN and MSI show distinct clinical and pathological features. Sporadic MSI tumors tend to be proximal and usually have a diploid phenotype whereas sporadic CIN tumors often have no site predilection and are aneuploid.

In 1993, seminal articles reported the presence of microsatellite instability (MSI) as a frequent molecular phenomenon in colorectal cancers (CRC). Since then, a plethora of studies applying various approaches have characterized this molecular subtype. Tumors harboring a deficient mismatch repair (MMR) system owing to germline, somatic or epigenetic inactivation account for 15-20% of CRC. MSI provides useful information in the prognosis of the colon cancer and also the prediction of response to chemotherapy or immunotherapy.

Recent clinical trials have showed that fluorouracil based adjuvant chemotherapy for stage II or III colon cancers with proficient MMR or low MSI/ MSS would be beneficial, but not for high MSI. The reason for this treatment specific response is related to individual cell cycle dynamics influenced by MMR signaling pathway (favoring apoptosis and diminuing proliferation), which contributes to the standard chemoresistance of cancer cells.

At Ho Chi Minh City Oncology Hospital, the immunohistochemistry test for MMR has been put into practice. However, applying this test in the real clinical pratice is still not standardized. That is why we performed this study.

PATIENTS AND METHODS

Purposes of study

To evaluate the rates of MMR manifestation (MMR proficient and deficient) and 4 IHC proteins on IHC stanning MLH1, PMS2, MSH2, MSH6.

To evaluate the patient baseline and clinical characteristics in the relation to MMR profiles.

To evaluate the impact of MMR testing in the change of patients' treatment decision.

Patients

Patients with pathologically confirmed stage II colon cancer (T3-T4N0M0) were hospitalised at our hospital from April 1st, 2017 until September 30th, 2017 (6 months). MMR status was assessed by using immunohistochemistry (IHC). All patients who had tissue specimens available for MMR IHC stanning [with the 4 kits: MLH1 (M1) PAB, PMS2 (EPR3974), MSH2 (G219-1129), COFIRM anti-MSH6 (44) mouse mono provided by VETANA company) would be enrolled. We excluded the patients without FFPE block, with no information for staging or refusing testing after being consulted about the test.

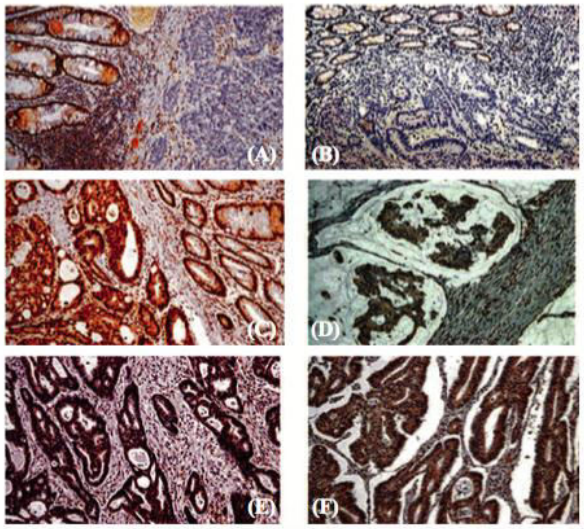

Fig 1. *Immunohistochemical staining of MMR gene proteins, x 200 magni cation.*
(A) Positive nucleus staining for MLH1 protein in normal colon (left) and absent staining in colon cancer (right).
(B) Positive nucleus staining for PMS2 protein in normal colon (upper) and absent staining in colon cancer (lower).
(C) Positive nucleus staining for MSH2 protein in normal colon (right) and colon cancer (left).
(D) Absent nucleus staining for MSH2 protein in mucinous carcinoma (left) and positive staining in brous stromal cells, as internal control (right).
(E) Scattered positive nucleus staining for MSH6 in colon cancer.
(F) Absent nucleus staining and weak cytoplasm staining for MSH6 in colon cancer.

After testing MMR status, the patients would be treated as planned in our hospital standard protocol. If stage II colon cancer patients have low risks and aged ≥65, proficient MMR would be consulted to receive adjuvant capecitabine or 5FU/LV, while the others with deficient MMR would receive no adjuvant chemotherapy.

We enrolled 46 suitable cases in 6 months.

Methods

This is a non-conventional cross sectional study (based on patient records) with logitudinal follow-up to evaluate survival later-on.

Data will be analyzed by using SPSS 17.0 (for Windows) and Stata 12.0 sofwares.

RESULTS

Patient baseline and clinical characteristics

Table 1. *Patient characteristics*

Characteristics	N=46 (%)
Age	
Medium	58.6
Range	33-87
Age-groups	
< 65 years old	34 (73,9%)
≥ 65 years old	12 (26.1%)
Sex	
Male	25 (54.3%)
Female	21 (44.9%)
Family history	
Colorectal cancers	5 (10.9%)
Other malignancies	3 (6.5%)
None	38 (82.6%)
Individual history	
Colorectal cancers	2 (4.3%)
GI polypsis syndrome or known HNPCC	4 (8.7%)
Chronic comorbidities (hypertension, diabetes, lung disease,…)	15 (32.6%)
Other diseases (operative, shorterm illness,…)	12 (26.1%)
None	13 (28.3%)

Table 2. *Clinico-pathology characteristics*

Characteristics	Number of patients (%)
Primary tumor location	
Right	15 (32.6%)
Left	31 (67.4%)
Tumor stage- pT (TNM stage)	
T3 (IIa)	16 (34.8%)
T4a (IIb)	22 (47.8%)
T4b (IIc)	8 (17.4%)
Pathology	
Ademocarcinoma	42 (91.3%)
Mucinous/ signet cell ademocarcinoma	4 (8.7%)
Histology grade	
G1	4 (8.7%)
G2	36 (78.3%)
G3	6 (13%)
Risk factors	
Yes	30 (65.2%)
No	16 (34.8%)
Risk groups	
Bowel obstruction	8 (34.8%)
No evaluation of lymph nodes or <10 lymph nodes evaluated	16 (34.8%)
Invasion of adjacent organs	6 (13%)
Neural/ vascular invasion	0

All of the low risk patients above have the histology grade 1 or 2.

Table 3. *MMR manifestation on IHC*

Characteristics	Positive n (%)	Negative n (%)
MLH1	38 (82.6%)	8 (17.4%)
PMS2	36 (78.3%)	10 (21.7%)
MSH2	41 (89.1%)	5 (10.9%)
MSH6	41 (89.1%)	5 (10.9%)
	Proficient n (%)	Deficient n (%)
MMR	32 (69.6%)	14 (30.4%)

In 14 cases of dMMR, 6 cases (14,3%) lost of 2 proteins MLH1 and PMS2 expression, 3 cases (6,5%) with lost of 2 proteins MSH2 and MSH6 expression (suspected for Lynch syndrome). There was 1 case with 3 proteins expression (MLH1, PMS2 and MSH2) and 1 cases with lost of expression of all 4 proteins.

Table 4. *MMR manifestation based on individual and family history*

Characteristics	pMMR	dMMR
Individual history		
CRC	1	1
Polypsis or HNPCC	4	0
Family history		
CRC	1	4
HNPCC or related cancer	0	0

There were 3 cases with family history of colorectal cancer, in accordance with Amsterdam criteria. 2 cases had the IHC manifestation

suspected for Lynch syndrome (co-lost of expression of MSH2 and MSH6 proteins). Further germline cell mutations should be done for these patients to confirm HNPCC. 1 patient had co-lost of expression of MLH1 and PMS2 proteins.

Table 5. *MMR manifestation based on primary tumor site and pathologic features*

Characteristics n (% on row)	pMMR	dMMR
Primary tumor sites		
Right colon	7 (46.7%)	8 (53.3%)
Left colon	25 (80.6%)	6 (19.4%)
Pathology		
Ademocarcinoma	30 (71.4%)	12 (28.6%)
Mucinous/ signet cell ademocarcinoma	2 (50%)	2 (50%)

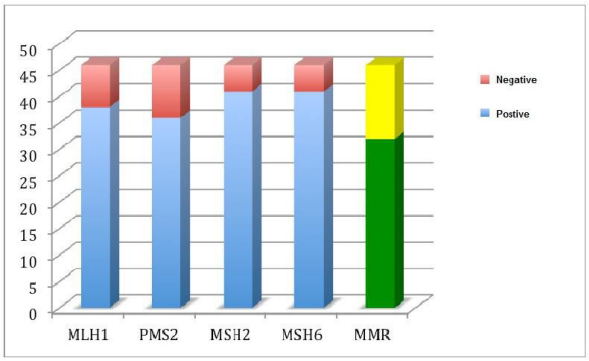

Fig 2*: MMR manifestation and related protein expression rates*

- *pMMR*
- *dMMR*

Treatment details

All the patients had curative surgery before entering our study.

Table 6*. Relation between adjuvant chemotherapy, MMR and risk factors*

			Adjuvant chemothetapy (n)	
			Yes	**No**
MMR	pMMR	High risk	21	1
		Low risk	10	0
	dMMR	High risk	6	2
		Low risk	1	5

There were 3 patients with high risk but did not receive chemotherapy because of old age (>65 years old) (one with pMMR) and/or comorbidities. One case with dMMR and low risk factors received CapeOX because there were 3 members of the family with CRC (her father and 2 brothers). Thus, MMR results helped to decide the chemotherapy for 15 cases (in 16 patients with low risk factors).

Table 7*. Chemotherapy regimens in relation with MMR and risk factors*

			Adjuvant chemo-regimens (n)	
			Capecitabine	**CapeOx**
MMR	pMMR	High risk	13	8
		Low risk	9	1
	dMMR	High risk	1	5
		Low risk	0	1

Thus, MMR testing help to choose fluorouracil based chemotherapy on 13 patients (61.9%) with pMMR result and high risk factor (one patients would not be able to choose oxaliplatin based chemotherapy because of comorbidities, old age or not willing to have infusion chemotherapy).

DISCUSSION

Molecular basis of the MMR system

Microsatellites are repetitive sequences distributed throughout the human genome and consist of mononucleotide, dinucleotide or higher-order nucleotide repeats. These sequence motifs are especially prone to accumulation of mutations, mainly due to slippage of polymerases during DNA synthesis. The most frequent errors associated with microsatellites are base-base mismatches that escape the intrinsic proofreading activity of DNA polymerases. Insertions or deletions in microsatellites located in DNA coding regions generate frameshift mutations leading to protein truncations[7].

The MMR system is responsible for the surveillance and correction of errors introduced in microsatellites and is highly conserved from bacteria to humans. MLH1, MSH2, MSH6 and PMS2 are the main proteins involved in this system, and they interact as heterodimers. Protein heterodimers of MutS homologues (MSH2, MSH6) and of MutL homologues (MLH1, PMS2) are sine qua non components of the human multimeric DNA MMR protein complexes that correct strand alignment and base matching errors during DNA replication. When any one of these MMR proteins is absent or nonfunc-tional, the MMR process malfunctions, as

reflected by length alterations in microsatellites, ie, microsatellite in-stability (MSI). Therefore, loss-of-function defects in MMR result in error-prone DNA replication and MSI.

CRC patients with dMMR tumor have distinct clinical and pathologic features, such as proximal colon predominance, poor differentiation and mucinous histology, with increased numbers of tumor-infiltrating lymphocytes. Tumors with dMMR are more common among stage II, and are relatively uncommon among metastatic CRCs. MMR-deficiency can arise from two distinct molecular alterations. Lynch syndrome (LS) accounts for approximately 3-4% of all CRCs and one third of all dMMR/MSI-associated CRC. It is inherited autosomal dominant and is caused by inactivating germline mutations in MMR genes, including MLH1, MSH2, and more rarely MSH6 and PMS2. Germline mutations in an MMR gene followed by a second hit to the wild-type copy is needed to produce LS, and can occur due to point mutation, loss of heterozygosity or methylation. Patients with LS develop tumors at early ages, often between 20 and 30 years old (compared to median age of 69 years in sporadic CRC) and have increased rates of synchronous CRCs. While cancers of the colon and rectum are most common among LS patients, these patients can also develop cancers of the uterine endometrium, stomach, ovary, urinary tract, small intestine and other sites. The estimated cumulative risks of CRC by age 70 years for LS patients is approximately 50% in case of MLH1 or MSH2 mutations, with endometrial cancer as the second most common malignancy in these patients. CRCs from LS patients are significantly less likely to carry BRAFV600E mutation. Among dMMR/ MSI CRCs, BRAFV600E mutation testing thus can be performed to distinguish LS cases from sporadic tumors. Patients with suspected hereditary CRC should be referred for genetic counseling, where the identification of germline mutations and evaluation/screening of family members can be appropriately addressed.

Among the 12-15% of all CRC tumors with dMMR/ MSI, about two-thirds are sporadics. The majority of these cancers develop in a background of dense promoter hypermethylation of cancer-specific genes known as the CpG island methylator phenotype (CIMP). CIMP-related silencing of the MLH1 gene is known to be responsible for about 80% of cases in which MLH1/ PMS2 expression are lost. Approximately half of sporadic dMMR cases are associated with BRAFV600E mutations that serve to distinguish them from LS cases. Patients with sporadic CRCs with MSI share clinicopathological features with LS cases with the exception that sporadics are substantially older at CRC diagnosis compared to LS and there is a female predominance.

Our study reports a series of 46 stage II colon cancer patients (≤50 years), for whom IHC staining was performed. Traditionally, clinical criteria such as the Amsterdam I/II and Bethesda criteria have been established to guide further gene testing in the diagnosis of Lynch syndrome and in identifying high-risk patients and families in the clinical setting and is useful in facilitating comparison between research studies. While these guidelines are useful tools, the flaws of using these criteria are well known with limited sensitivity and specificity. In addition, these criteria were established based on Caucasian populations, and may not be appropriate when applied to an Asian population as phenotypic, molecular and histopathological features may vary between different ethnic groups. Routine MSI testing in familial and sporadic CRC is expensive, labour intensive, requires expert pathologic examination, microdissection and amplification of a panel of genetic markers. Although it has become cheaper and easier to perform and is a highly sensitive indicator of defective mismatch repair, it needs to be complemented by germline testing for the offending MMR gene defect in cases of MSI-H and would require genetic counselling of affected individuals. Such services may not be widely available. At present, it remains unclear whether any one set of criteria can be applied uniformly to distinct populations likely to have different genetic and environmental risks.

Amsterdam II criteria- families must fulfill all criteria[2,15]:

1. There should be at least 3 relatives with an HNPCC-associated cancer (colorectal, endometrium, stomach, small bowel, ureter or renal pelvis).

2. One should be a first-degree relative of the other 2.

3. At least 3 successive generations should be affected.

4. At least 1 should be diagnosed before age 50.

5. FAP should be excluded in the colorectal case(s), if any.

6. Tumours should be verified by pathological examination.

In our study on stage II colon cancer patients, there were 3 cases (6.5%) which were suspected for Lynch syndrome (compatible with Amsterdam II criteria). 2 patients with lost of both MSH2 and MSH6

expression, and need to have germline gene mutation testing to confirm the diagnosis of LS.

Testing for MSI and MMR defects

Detection of MSI

MSI is detected by PCR amplification of specific microsatellite repeats (markers). The presence of instability is determined by comparison of the length of nucleotide repeats in tumor cells and normal cells. Normal DNA is typically extracted from adjacent normal mucosa. In the late 1990s, a consensus conference established a panel of microsatellite markers with appropriate sensitivity and specificity to diagnose MSI CRC. This reference panel, known as the Bethesda panel, included five microsatellite loci—two mononucleotides (BAT25 and BAT26) and three dinucleotides (D5S346, D2S123 and D17S250). Some clinical and research laboratories have expanded this panel to ten markers. Three categories of MSI have been established based on the following criteria: MSI-high (MSI-H), indicating instability at two or more loci (or >30% of loci if a larger panel of markers is used); MSI-low (MSI-L), indicating instability at one locus (or in 10-30% of loci in larger panels), and microsatellite stable (MSS), indicating no loci with instability (or <10% of loci in larger panels). MSI-L cases usually only show instability for dinucleotide markers, so the assessment of dinucleotides alone could lead to the misclassification of MSS or MSI-L CRC as MSI-H. On the contrary, mononucleotides BAT25 and BAT26 are nearly monomorphic, so in the absence of normal control tissue, MSI determination could be based entirely on these. Therefore, the Bethesda panel has a sufficient combination of markers for MSI detection, but newer commercial kits now include a predominance of mononucleotide markers with improved sensitivity. [7]There are some limitations for MSI testing. Firstly, the procedure needs many resources, especiallly specialised pathologists. Moreover, tissues for amplification need to be processed and cut in micro slides to avoid DNA amplification from normal colon epithelial cells.

Immunohistochemistry for MMR testing

Immunohistochemical analysis of MMR proteins has become a popular alternative to detect MSI in the clinical setting and as a complement to the genetic testing of Lynch syndrome. Antibodies against MLH1, MSH2, MSH6 and PMS2 proteins provide insight into the functionality of the MMR system. Lack of expression of one or more of these proteins is diagnostic of deficient MMR, and determines which gene is most likely to harbor a germline mutation or to have been inactivated by another mechanism. Interpretation of the immunohistochemical pattern takes advantage of the dependent expression of specific heterodimers in the molecular diagnostic workup of CRC. As an example, CRCs that lack expression of MLH1 and PMS2, but retain expression of MSH2 and MSH6, represent deficient MLH1 expression. In this situation, absent expression of PMS2 is simply a consequence of the defective MLH1. Whether the deficiency of MLH1 is caused by inactivation of the gene by promoter hypermethylation or a germline mutation that causes Lynch syndrome requires further investigation, but immunohistochemistry directs the workup to concentrate on MLH1 rather than the other MMR genes.

The understanding of how the MMR proteins interact during DNA repair can help in the interpretation of the results of such testing. MSH2 forms a heterodimer with MSH6, while MLH1 binds to PMS2 and complexes MSH2/ MSH6 heterodimer. Therefore, when MSH6 is not detected in a tumour MSH6 may also not detected. The situation is more complex with lack of MLH1 expression. Hypermethylation of hMLH1 gene, which is common in sporadic colorectal cancer, may lead to loss of protein expression.

Analysis of MMR protein expression by immunohistochemistry (IHC) is an alternative test that is widely available with the advantages of not requiring a molecular laboratory and the ability to identify the affected gene by detecting loss of its protein product. Since the loss of MMR protein expression by IHC has been shown to be highly concordant with DNA-based MSI testing, these two tests are considered to be complimentary. Using IHC, tumors that demonstrate loss of an MMR protein can be collectively referred to as dMMR and expected to be MSI-H. Importantly, only loss of hMLH1 protein expression has been described in sporadic CRCs. Tumors with intact MMR proteins can be classified as proficient MMR that are MSS or MSI-low (MSI-L).

IHC has a role in detecting MMR defects, with data suggesting that the effectiveness of IHC screening of the MMR proteins would be similar to that of the more complex strategy of microsatellite genotyping. This technique can guide which gene to sequence and can help differentiating sporadic from hereditary mutations: MSH2 loss is likely to be HNPCC, whereas MLH1 loss could be HNPCC or sporadic CRC (MLH1 promoter methylation). MMR proteins heterodimerize to function; the MSH2 loss almost always accompanies MSH6 loss and when MLH1 is lost, generally so is hPMS2. In addition, IHC

can miss functional loss; i.e. presence of the protein with antigen positivity in the absence of function.

MMR IHC studies are based on a complete absence of at least one MMR protein. But these studies do not consider the immunostaining topographic heterogeneity. Since the MMR proteins function as heterodimers, it could be advocated to validate the IHC results of MSH2/ MSH6 and MLH1/ PMS2. More studies are required to clarify the in uence of this predictable tumor heterogeneity to select the appropriate sample for immunohistochemical and/or MSI analyses[11].

Thus, in our study, the choice of IHC in order to establish the MMR manifestation without MSI testing (based on PCR) is suitable in the clinical practice. With MMR testing, we could consult for about 30.4% stage II colon cancer patients not to choose adjuvant fluorouracil based chemotherapy (no risk factors).

In the results, we found that lost of both MSH2-MSH6 expression (6.5%) and MLH1-PMS2 (14.3%) was most common. This finding is also compatible with literature.

Gene expression profiling of MSI tumors

Multiple methods have been used for genetic testing in HNPCC. The methods used should ideally be able to detect the many potential genotypes associated with HNPCC like nonsense, missense, and frame shift mutations, genomic deletions, duplications, and rearrangements. The commonly used tests includes: high output screening techniques, DNA sequencing, conversion analysis and methods to detect large structural DNA abnormalities like Southern blot and Multiplex ligation-dependent probe amplification.

Now, HCMc University of Medicine and Pharmacy could perform gene sequencing to identify Lynch syndrome. So with our study, we could see that MMR testing is the screening test to look for suitable candidates of Lynch syndrome gene testing.

Features and applications of MSI on stage II colon cancers

A recognizable clinicopathological profile of MSI tumors has been established from clinical studies. CRC displaying MSI tend to be right-sided and diagnosed at lower pathological stages compared with MSS cancers. Regarding the age at diagnosis, sporadic MSI cases are generally diagnosed in older patients (>70 years of age), and familial cases are younger (<50 years of age) and show a U-shaped age distribution. Under the microscope CRC generally have high histological grades, mucinous phenotypes with prominent numbers of tumor-infiltrating lymphocytes, a lack of dirty necrosis and a Crohn-like host response. These features can be successfully combined to predict the likelihood of the presence of MSI in tumor samples[7].

The MSI phenotype has three major clinical applications. Prognosis of CRC, prediction of response to chemotherapeutic agents, such as 5-FU and irinotecan, and genetic assessment of Lynch syndrome[7].

Prognostic value of MMR in CRC

Although the pathologic tumor stage remains the key determinant of CRC prognosis and treatment, there is considerable stage-independent variability in clinical outcome. Thus, new prognostic and predictive biomarkers are needed to inform prognosis and to guide the use and choice of systemic chemotherapy. Accumulating evidence indicates that dMMR status is one such candidate.

Gryfe et al. reported the first cohort of patients in whom the prognostic importance of defective MMR was demonstrated. MSI tumors had a more favorable prognosis and were less prone to lymph node and distant metastatic spread than MSS tumors. [15]These results have been corroborated by many subsequent studies, such as that in the large series reported by Watanabe et al. Individual clinical data from a total of 32 studies were considered in a meta-analysis that included 7,642 cases, where 1,277 of these displayed MSI. The meta-analysis confirmed the prognostic advantage of MSI, and also showed a better prognosis for patients with dMMR compared with pMMR tumors. [2,14]Moreover, a presentation at the ASCO 2009 Annual Meeting reported that the prognostic value of MSI is more prominent in stage II than stage III cases. Despite the reproducibility of these data, they have not been routinely incorporated into practice for MSI to inform patients about their prognosis or to guide therapeutic decision-making.

In our study, we chose stage II colon cancer patients to test for MMR expression. However, the follow-up time would not be long enough to evaluate long-term outcomes.

MMR status and 5-FU based adjuvant chemotherapy

The fluoropyrimidine 5-FU remains the most commonly used chemotherapy drug for the treatment of CRC. Where adjuvant chemotherapy remains optional in stage II CRC patients, capecitabine or 5-FU combined with leucovorin (LV), or combinations of these drugs with oxaliplatin, are considered to be standard treatment options for stage III. Preclinical models have suggested that dMMR tumors were associated with 5-FU resistance. The preponderance

of evidence also suggests that 5-FU-based adjuvant chemotherapy is ineffective in patients with dMMR tumors, although some earlier studies suggested that patients with dMMR vs. pMMR tumors derive a similar or even a greater benefit from 5-FU-based adjuvant treatment. Conflicting results were based on studies where patients were not randomly assigned to 5-FU-based treatment versus observation after resection, a relatively small numbers of patients with dMMR colon cancers, and the bimodal age distribution among these patients. Accordingly, the impact of dMMR status as prognostic/predictive classifiers is ideally studied to a clinical trial cohort of same stage patients receiving uniform treatment.

Sargent et al. investigated 457 stage II and stage III colon cancer patients who were included in ve randomized trials evaluating 5-FU + levamisole or LV as adjuvant chemotherapy vs. no post surgical treatment. In this analysis, patients with dMMR cancers had significantly better survival than did pMMR patients, although dMMR tumors of either stage did not benefit from 5-FU-based adjuvant therapy. [2,5]These findings were validated by combining these data with those from a prior study by Ribic et al. from the same group, yielding a total of 1,027 stage II and stage III colon cancer patients. In the combined dataset, dMMR was associated with more favorable outcome compared to pMMR cancers (DFS: HR=0.51; 95% CI, 0.29-0.89; P=0.009; OS: HR =0.47; 95% CI, 0.26-0.83; P=0.004), and 5-FU adjuvant chemotherapy may attenuate the prognostic advantage of dMMR (DFS: HR=0.79; 95% CI, 0.4-1.25; P=0.30; OS: HR=0.78; 95% CI, 0.49-1.24; P=0.28). Of note, a suggestion of a detrimental effect of 5-FU was seen in patients with stage II dMMR tumors. These data were interpreted to indicate that patients with dMMR stage II CRC should not receive adjuvant 5-FU[11].

A lack of efficacy for 5-FU as adjuvant chemotherapy in patients with dMMR stage II CRC was observed in the Quick and Simple and Reliable (QUASAR) adjuvant therapy trial where patients with stage II CRCs were assigned to receive 5-FU (n=1,483) vs. surgery alone (n=1,480). Among all patients with known MMR status, the risk of recurrence of dMMR tumors was reduced by half compared to pMMR tumors [11% (25 of 218) vs. 26% (438 of 1,695) recurred; risk ratio (RR)=0.53; 95% CI, 0.40-0.70; P<0.001]. However, MMR status did not predict bene t from chemotherapy (HR=0.97, P=0.92). More recently, the prognostic impact of dMMR in stage II and III CRC patients was further examined using pooled data analysis from 17 adjuvant trials in the ACCENT database. This analysis involved 7,803 patients of which 571 received surgery alone and 3,878 patients received 5-FU monotherapy. Among stage II patients, dMMR vs. pMMR was strongly associated with increased TTR (HR=0.27; 95% CI, 0.10-0.75; P=0.01) and improved OS (HR=0.27; 95% CI, 0.10-0.74; P=0.01) in patients treated with surgery alone. However, such advantage of dMMR over pMMR was attenuated in patients treated with adjuvant 5-FU (TTR: HR=0.81, 95% CI, 0.55-1.19; P=0.29; OS: HR=0.87; 95% CI, 0.61-1.26; P=0.47). Among stage III patients receiving surgery alone, those with dMMR tumors were also found to have better outcome (TTR: HR=0.59; 95% CI, 0.28-1.23; P=0.16; OS: HR =0.69; 95% CI, 0.35-1.36; P=0.28) vs. pMMR cases. In stage III CRC patients, a significant survival bene t for 5-FU monotherapy vs. surgery alone was seen in patients with pMMR tumors (5-year TTR=64% vs. 47%), but also in patients with dMMR tumors (5-year TTR=72% vs. 60%). These findings support the current and recommended management of non-metastatic CRC whereby stage II patients with dMMR tumors are spared adjuvant 5-FU due to lack of ef cacy, whereas all stage III patients received adjuvant chemotherapy irrespective of MMR status.

In a study that evaluated 2,141 stage II and stage III colon cancers from 5-FU-based adjuvant therapy trials, patients with dMMR colon cancers were shown to have reduced rates of tumor recurrence, delayed TTR, and improved survival rates compared with patient with pMMR cancers. Furthermore, an exploratory subset analysis suggested that dMMR tumors with suspected germline mutations (i.e., LS) had improved disease-free survival (DFS) after 5-FU-based treatment (DFS: HR=0.26; 95% CI, 0.09-0.77; P=0.009) compared with sporadic dMMR tumors where no benefit was observed (DFS: HR=0.79; 95% CI, 0.35-1.80; P=0.58). These preliminary findings raise the possibility that the utility of MMR status as a predictive factor for 5-FU treatment might differ according to the molecular mechanism underlying dMMR/MSI, which awaits further evaluation[2].

Treatment with standard 5-FU plus oxaliplatin adjuvant therapy

At present, the use of oxaliplatin in combination with adjuvant 5-FU chemotherapy is the standard of care for stage III colon cancer patients. Preclinical studies have shown that dMMR tumor cells are susceptible to oxaliplatin despite displaying resistance to 5-FU. To date, limited data are available for the prognostic/predictive impact of MMR on chemosensitivity to oxaliplatin-based treatment. In a retrospective study that included 303 unselected

stage III colon cancer patients who received adjuvant FOLFOX, MMR status was a prognostic factor conferred a better DFS for patients with dMMR compared to pMMR tumors. Gavin et al. reported an analysis of 2,299 stage II and stage III colon cancers from participants in National Surgical Adjuvant Breast and Bowel Project (NSABP) adjuvant studies, including C-07 (5-FU plus LV ± oxaliplatin) and C-08 (FOLFOX ± bevacizumab) trials. The authors reported that dMMR was associated with better prognosis for recurrence in patients treated with FOLFOX compared with pMMR (TTR: HR=0.58; 95% CI, 0.35-0.96; P=0.03). However, MMR status was not predictive of oxaliplatin efficacy, since the interaction test between MMR status and treatment was not statistically signi cant. Flejou et al. reported the results of MMR status in 986 of the 2,240 patients enrolled in the Multicenter International Study of Oxaliplatin/5-FU LV in the Adjuvant Treatment of Colon Cancer (MOSAIC). The authors found that the DFS benefit from FOLFOX compared with 5-FU alone was also evident in patients with dMMR colon cancers (52). Taken together, available data suggest a potential benefit for oxaliplatin in node-positive dMMR colon cancers and therefore, do not support any change in the current therapy of these patients[2,3].

Based on medicine literature and international practical guidelines (ESMO, ASCO and NCCN), we contributed to build up an agreement of stage II colon cancer. For high risk stage II colon cancer patients, oxaliplatin and 5FULV (or capecitabine) based chemotherapy are considered, while the low risk patients underwent with no further treatment if the MMR test is deficient. Thus, there were 15 low risk patients and 13 high risk patients (# 60.9%) who were consulted to choose an appropriate treatment. However, we need to follow up this group of patients for survival analysis. We also have to cooperate other factors (i.e, BRAF, CDX2,…) in the prognosis and the prediction of therapy sensitivity.

CONCLUSION

According to the evaluation of MMR expression on 46 stage II colon cancer patients, we had some results:

- dMMR is on 14 patients (30.4%), most of cases are lost of both MLH1-PMS2 expression (14.3%). 6.5% cases lost of both MSH2-MSH6 expression (14.3%) (suspected for Lynch syndrome).

- There were 3 cases fulfilled Amsterdam II criteria and MMR testing showed possible Lynch syndrome and need for germline genetic sequencing.

- dMMR is more often on right colon cancer, mucinous type of adenocarcinoma.

- Based on the results of MMR, there were 28 patient (60,9%) was consulted to lean toward appropriate adjuvant treatment.

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INITIAL FINDINGS: NEO-ADJUVANT CHEMORADIOTHERAPY COMBINED WITH SURGERY IN TREATMENT OF STAGE II – III RECTAL CANCER

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ABSTRACT

Neo-adjuvant Chemoradiotherapy has become the standard treatment for locally advanced rectal cancer. The study has been implemented in HCMC Oncology Hospital and based on stage II-III middle and low third rectal cancer patients, divided into two groups: Clinical research and Historical control. Clinical research (CR) of 119 patients follows Neo-adjuvant Chemoradiotherapy combined with surgery regimen. Historical control (HC) of 104 patients follows surgery combined with Post-operation Chemoradiotherapy regimen. The first endpoint is One month after operation. The second endpoint is two years after operation. Radical tumor resection rates of the two CR and HC groups are 96.8% and 77.9% (P value <0.001). Sphincter preservation rates are 73.9% and 55.8% (P value <0.001) respectively. On the low third rectal cancer patients, sphincter preservation rates are 56.9% and 29.8% (P value <0.001) respectively. There are no significant differences in blood loss, operation time, complications and mortality between two groups.

OPENING STATEMENT

Rectal cancer is the fifth most popular cancer types in Vietnam and the third in US. There are about 40,000 new cases diagnostied every year in US.

The very challenge in treatment of this disease is to reduce local recurrence and performing the sphincter preservation to improve post-operation living. TME has proved its effective impact in local recurrent reduction. However, in stage II–III patients, local recurrence rate can be upto 50% following operation.

Since 1970, researches such as GITSG 7175 (Gastrointestinal Tumor Study Group), NCCTG 79475 (North Central Cancer Treatment Group), Mayo/ NCCTG, NSABP R-02 (National Surgical Adjuvant Breast and Bowel Project) have proved the efficiency of Post-operation chemoradiotherapy with 34% reduction in the local reccurence rate, particularly in stage II–III patients. In 1990, NCI (National Cancer Institute) published “Rectal cancer Treatment Consensus.”, in which multi-modality has become new standard treatment in rectal cancer.

German Rectal Cancer study group’s CAO/ARO/AIO-94 trial compared the effectiveness of Neo-adjuvant chemoradiotherapy and post-operative chemoradiotherapy in 823 cases. Their findings showed Neo-adjuvant chemoradiotherapy help reducing local reccurence (6% vs 13%), acute side effect (27% vs 40%) and chronic side effect (14% vs 24%).

At Bach Mai Hospital and Ha Noi K Institute, the prospective case study of Pham Cam Phuong in 65 locally advanced rectal cancer patients showed promising results: 9.2% with pathology complete response; 93.1% down-staging tumor; 53.8% radical surgery; 15.4% sphincter preservation.

At HCMC Oncology Hospital, we have been implementing post-operative chemoradiotherapy in stage II–III rectal cancer treatment since 1990. This has brought positive results with 7.3% of 2-year local reccurence and 40% of sphincter preservation. We have since pushed forward in improving treatment efficacy. With the prospect of possible better result of Neo-adjuvant chemoradiotherapy comparing to Post-operative chemoradiotherapy, using in-hands facilities at HCMC Oncology Hospital, we started trial to compare the two methods in stage II–III rectal cancer treatment. The final results have been closely tracked and would be updating upon midlle of 2018. We now present the initial findings of 20-month follow-up.

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OBJECTIVE AND METHODOLOGY

OBJECTIVE

Patients: Diagnosted with stage II–III middle-low rectal cancer; Adeno-Carcinoma Pathology; Admited to Surgical Department II from June 2014 to December 2015.

METHODOLOGY

Study structure

Clinical trial with historical control.

Eligibility for enrollment

- Clinical trial

Patients diagnosted with stage II–III middle-low rectal cancer; with Adeno-Carcinoma Pathology; admitted to Surgical Department II from June 2014 to December 2015; consenting in joining study group in written form.

- Historical control

Patients diagnosted with stage II–III middle-low rectal cancer; treated with operation and Post-operative chemoradiotherapy; admitted to Surgical Department II from January 2014 to May 2014 and Patients who chose to go for operation first, from June 2014 to December 2015.

We conducted the sample size of minimum 100 cases each group.

Eliminating criteria

Pathology other than adeno-carcinoma.

Bowel obstruction, peritonitis caused by tumor perforation.

Not-consenting in joining study group.

Carcinomatosis findings via surgical performance.

Patients must follow the treatment protocol strictly. All data are to be collected and analyzed using SPSS 22.0. The first endpoint is one month after operation day. The second endpoint is 24 months after operation day.

RESULTS

Table 1. *Characteristics of eligible patients*

Characteristic	Study Group (N=119)	H. Control (N =104)	Fisher'exact/ P value
Age-year			0.470
Median	55	57.5	
Range	23-90	25-87	
Gender-no. (%)			0.689
Male	54 (45)	52 (50)	
Female	65 (55)	52 (50)	
Distance of tumor from anal verge-No. (%)			0,8
≤ 5cm	59 (49)	50 (48)	
>5-10cm	60 (51)	54 (52)	
Stage-No. (%)			
II	31 (26)	36 (35)	0,17
III	88 (74)	68 (65)	0,17
T4	59 (49)	42 (40)	0,2

Table 2*. Neo-adjuvant Chemoradiotherapy*

Variable	Result
Chemotherapy-No. (%)	
Capecitabine	84 (71)
5-FU	35(29)
Clinical response-No. (%)	
Non-change	8(7)
Partial response	88 (74)
Near complete response	21 (18)
Complete response	2 (2)
Pathology response	
TRG 1	22 (19)
TRG 2- 5	97 (81)

Operation

Table 3. *Types of surgery*

Type-No. (%)	Study Group (N=119)	H. Control (N=104)	
Unresectable	0	20 (19)	
Low anterior resection	75 (63)	58 (56)	P=0.000*
Ultralow A.R	13 (11)	0	Fisher's exact
Hartmann Procedure	2 (2)	5 (5)	
APR	27 (23)	21 (20)	
Pelvectomy	2 (2)	0	

Table 4. *Types of surgery for tumors with distance to anal verge ≤ 5cm*

Type-No.(%)	Study group (N=65)	H. Control (N=47)	
Unresectable	0	11 (23)	P=0.000* Fisher's exact
Low anterior resection	26 (40)	14 (30)	
Ultralow A.R	11 (17)	0	
Hartmann Procedure	0	3(6)	
APR	27 (41)	19 (40)	
Pelvectomy	1 (2)	0	

Table 5. *Resection margin*

Resection Margin	Study Group (N=119)	H. Control (N=104)	
Unresectable	0	20 (19)	P=0.000* Fisher's exact
R0	115 (97)	81 (78)	
R1	3 (2)	2 (2)	
R2	1 (1)	1 (1)	

Table 6. *Operation duration*

Time-minute	Study Group	H. Control	P (unequal variance)
Low anterior resection			0,067
Median	120 ± 41,8	109,6 ± 27,8	
Range	75-240	50-120	
N	75	53	
APR			0,204
Median	133 ± 27,9	122 ± 28.1	
Range	100-230	80-190	
N	27	21	
Hartmann Procedure			0,542
Median	117,5 ± 24,7	109 ± 15,9	
Range	100-135	85-120	
N	2	5	

Table 7. *Blood loss*

Blood loss - ml	Study Group	H. Control	P(unequal variance)
Low anterior resection			0,572
Median	70	70	
Range	10-300	20-200	
APR			0,374
Median	100	120	
Range	15-300	40-500	
Hartmann Procedure			0,093
Median	125 ± 35,3	90 ± 14.1	
Range	100-150	75-100	

Table 8. *Complication events*

Events-No. (%)	Study Group (N=119)	H. Control (N=104)	
Anastomosis Leakage	2 (2)	2 (3)	
Bowel Obstruction	3 (2)	3 (3)	
Necrosis of Artificial Anus	1 (1)	0	
Recto-vaginal Fistular	1 (1)	1 (2)	
Intestino- perineal Fistular	1 (1)	0	0

DISCUSSION

Characteristics of eligible patients

According to Claes et al, variables that strongly affect the treatment effectiveness include age, sex, tumor location, and stage of disease. We have found no significant differences in observing each characteristic of the two groups. Thanks to the findings, we can confirm the comparation between two groups is not be effected by such possible biases.

Neo-adjuvant Chemoradiotherapy

Chemotherapy

Patients in the study group received either adjuvant FU or Capecitabine chemotherapy in radio sensitivity enhancement. There were no differences in response and side effects between the two adjuvant choices. However, it is considered more convenient and safer with Capecitabine.

Common side effects are diarrhea and perineal dermatitis in slight occurrence (grade 1), not a significant problem to the overall treatment. There has not been any myelosuppression observed in this entire regimen study.

Assessment of chemoradiotherapy response

Clinical standard in evaluating the response of chemoradiotherapy in rectal cancer is post-operative pathology. Respective researchers have suggested the chemoradiotherapy response in 5 tumor regression grades: TRG 1–no cancer cell; TRG 1-few cancer cells residue; TRG 2–cancer cells less than fibrosis cells.; TRG 4–cancer cells more than fibrosis cells; TRG 5–only cancer cells found.

Disease-free and complete survival rate on TRG 1 patients has frequently reached above 90%. In this particular study, we have had 22 cases with complete response–post-operative pathology base, reaching 18.5% of the study body. This outcome is not alienated to those of other respective researches. (TRG).

Surgery treatment

Radical surgery

In treating locally advanced rectal cancer, surgions perform radical resection to remove all tumor structure and lymph nodes. Surgery clarity has commonly been classified into 3 degrees: R0- no tumor cell in pelvic cavity; R1- there are tumor cells in pelvic cavity at microscopic level; R2- there are tumor cells in pelvic cavity at macroscopic level. Radical resection is used to define a successful rectal cancer treatment. Otherwise, patients are facing possible morbidity and mortality.

Successful operation rates are 100% and 80.8% respectively in study group and historical control group. In this clinical study, we have found surgical clarity R1 in 3 cases (2.4%), R2 in 1 case (0.8%); and R1 in 2 cases (1.9%), R2 in 1 case (0.9%) with the other group. These incidents reduced the actual radical resection rate to 96.8% and 77.9% with 0.001 P value in the two groups.

At this stance, neo-adjuvant chemoradiotherapy has identified its efficacy in improving stage II–III rectal cancer radical resection.

Sphincter Preservation Surgery

It is considerably difficult to perform sphincter preservation surgery on one-third middle and low, stage II–III rectal cancer patients. The reason is to ensure a negative resection margin with the minimum distal margin of 3cm and to perform a challenging anastomosis procedure in a narrow pelvic cavity, using costly equipments. Neo-adjuvant chemoradiotherapy improved tumor and lymph nodes regression, reduced local recurrence and shortened the distal cutting margin below 1cm while maintaining negative resection margin.

The sphincter preservation was completed for 88 patients (73.9%) and 58 patients (55.8%) in the study group and the historical control group relatively at P value less than 0.001. In cases with tumor positioned less than 5cm from anal verge, the sphincter preservation was successfully implemented on 37 patients (56.9%) and 14 patients (29.8%) respectively in the two groups with P value less than 0.001. These outcomes have suggested the improvement in sphincter preservation possibility of neo-adjuvant chemoradiotherapy.

Possible surgical complexity and complications

Radioation was logically considered increasing anastomosis leakage due to its small-vein-fibrosis impact, at the same time increasing operative bleeding and damaging neighboring pelvic organs with its fibrosis effect. In the four weeks following

radiotherapy, radiation still actively involved in tumor regression. It took about six to eight weeks to reduce inflamatory congestion in the pelvic area. Fibrosis has shown its impact not as severe at this time as later from the twelfth week.

We decided that the operation timing should be within the sixth to eighth week following radiotherapy. This proved to be an appropriate decision in facilitating next-step operations with clear anatomical focal points, clean operative field thanks to fibrosis of small vessels. We have pushed it further in successfully performing relevant laparoscopic procedure for 28 patients (23.5%) who were able to finance such operation. Comparing operative variables such as average operation time, blood loss, complication events of the two groups, we have come to conclude that neo-adjuvant chemoradiotherapy does not increase surgical risk.

CONCLUSION

In conclusion, neo-adjuvant chemoradiotherapy in stage II–III rectal cancer treatment enhances the possibility of radical resection and sphincter preservation, and is not in jeopardy of surgical risk.

We are to see updates in two-year disease-free survival rate and overall survival rate of the study group.

We strongly suggest this regimen to be standardized in locally advanced rectal cancer treatment.

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MODIFIED UNIPORTAL VIDEO ASSISTED THORACIC SURGERY: THE FIRST 30 CASES

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ABSTRACT

Background: *The acceptance of uniportal video-assisted thoracic surgery (VATS) for minor and major thoracic procedures is growing in all of the world. This study presents the first experience with modified uniportal VATS (i-VATS) at HCMC Oncology hospital in Viet Nam.*

Methods: *In a retrospective study of prospectively collected data, 30 modified uniportal VATS (i-VATS) were analyzed between 12/2016 and 06/2017. The technique was used for diagnostic aims, tumorectomies, wedge resections, and anatomical lobectomies. All procedures were performed without rib spreading. Patients' demographic data, preoperative and postoperative management as well as results were analyzed.*

Results: *A total of 30 patients, among them 16 patients (53%) were males. The mean age was 52.3 ± 12.9 (25-70) years. The i-VATS procedures included wedge resections in 3 cases (10%), tumorectomies in 3 cases (10%), biopsies in 6 cases (20%) and other anatomical lobectomies in 18 cases (60%). The median operation time was 243, 105, 58, and 80 minutes for lobectomies, wedge resections, biopsies, tumorectomies, respectively. There were one conversions in case of middle lobectomie. The mean chest tube duration was 3 days. The mean hospital stay was 4-5 days for the whole group.*

Conclusions: *modified Uniportal VATS is a feasible and safe technique for various indications in thoracic surgery. The perioperative results are promising. It can be performed by thoracic surgeons experienced in the lateral thoracotomy approach.*

Keywords: *Video-assisted thoracic surgery (VATS); uniportal VATS; single-port thoracic surgery; minimally invasive thoracic surgery.*

INTRODUCTION

Uniportal Video Assisted Thoracic Surgery was described initially by Rocco at el[1] for minor thoracic and pulmonary procedures in 2004. Since then, many innovations have been done to improve the technique to the point where major anatomic resection is performed by this technique. The implementation of uniportal technique into the clinical practice is spreading globally[5,13,14].

The modified uniportal VATS was processed at Ho Chi Minh Oncology hospital since December 2016. The purpose of this study was to critically analyze the first preliminary experience on uniportal VATS at our hospital, in order to contextualize it internationally and understand its benefits and disadvantages.

PATIENTS AND METHODES

In this study, data for 30 patients who had undergone modified uniportal VATS procedure were collected retrospectively from December 2016 up to June 2017 in the Department of General Surgery, Ho Chi Minh Oncology Hospital.

The main endpoint of this study was the feasibility of this technique for thoracic surgeons mainly performing a lateral thoracotomy approach for major lung resections but experienced in minor VATS procedures. The outcome of uniportal VATS in terms of morbidity, 30 days mortality, conversion rate, operative time and hospital stay was studied.

Surgical technique

Under general anesthesia, the patients were intubated with double lumen endotracheal and placed in lateral decubitus position (Figure 1) with the

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bed maximally flexed and the breakpoint just above the superior iliac crest. This helps spread the intercostal spaces.

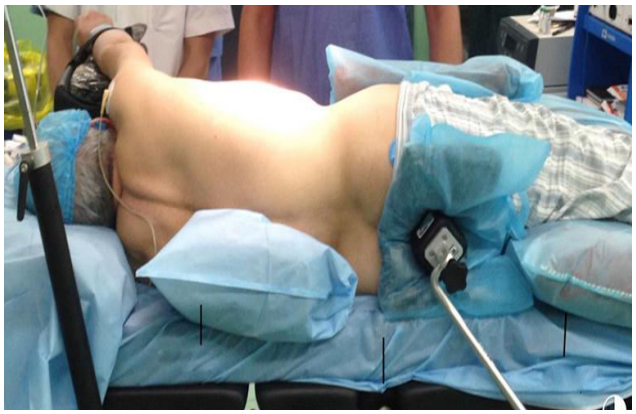

Figure 1. *Lateral decubitus position*

Both the surgeon and the assistant are positioned in front of the patient in order to have the same thoracoscopic vision during all steps of the procedure, thus allowing more coordinated movements. The scrub nurse should be positioned behind the patient (Figure 2).

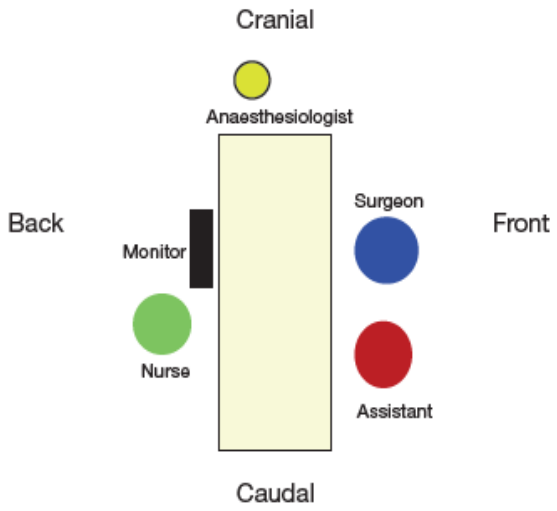

Figure 2. *Positioning of the surgical team during the operation*

The single incision, 3-4cm, was made in the mid axillary line of the 5th intercostal space. Rib retractors were not used during the procedures.

Then the 30 degree scope was introduced through one trocar which was placed above the main incision 1cm in the same intercostal. This trocar would keep the scope stable when the main surgeon manipulate as well as keep the surface of scope clean after introducing. This incision was modified and called “i” shape incision (i-VATS).

We used most of conventional equipment such as Yankauer sucker, soni-scissor and available instruments.

Because of lacking experiences, we didn’t perform lymph node dissection in these cases. All tumor specimens were removed with a nylon bag. At the end of the operation one 24 Fr chest tube was inserted in the place of trocar and then be fixed. The main incision was sutured layer by layer as usual (figure 3).

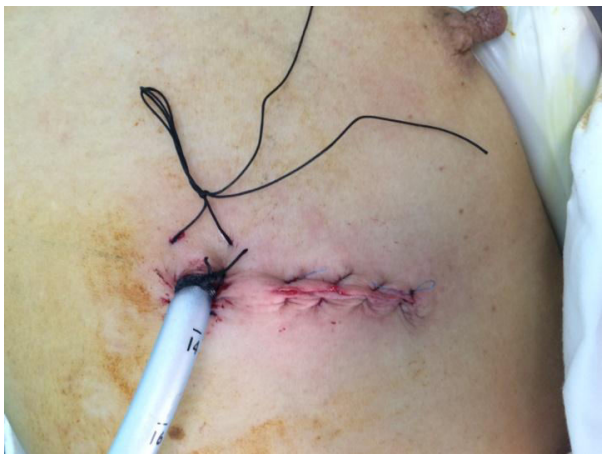

Figure 3. *The “i” shape incision*

Post-operative management.

Patients were admitted to the care unit and the next day to the normal ward. All of them received pain medication and 1.5 liter of fluid for 24 hours. Thoracic X ray was performed on 2nd or 3rd postoperative days. The thoracic drainage was removed after clamping for 2 hours nor secretion below 200ml within 24 hours. Patients were discharger on the same day.

Statistical analysis.

Data was conducted as mean values by Stata 16.0 and the significance level for all analysis was set at a P value of less than 0.05.

RESULT

Characteristics of patients

Between December 2016 and June 2017, there were 30 modified uniportal VATS procedures perform for different indications. There were 16 (53.33) males and the mean age were 52.3 ±12.9 years. In 16 (53.3) of the patients, the histological findings were malignant. All of our patients have good conditions of pulmonary functions preoperatively.

Table 1. *Characteristics of patients*

Age	52.3 ± 12.9 (25-70)	
BMI	21.03 ± 2.61 (14.5-25.65)	
KPS	80-90	
Pulmonary Fuctions		
FEV1	90.82 ± 13.7 (56-119)	
FVC	87.35 ± 12.71 (53-112)	
Arterial Blood Gas Analysis		
PO2	99.08 ± 16.51 (47-132)	
PaCO2	35.25 ± 2.97 (30-41)	
Gender	**Male**	**Female**
	16 (53.33%)	14 (46.67)
Smoking	**Yes**	**No**
	9	17
Benign/Malignance	14/16	

Table 2. *Location of tumor*

Location		Number
Right lung	Upper lobe	9
	Middle lobe	3
	Lower lobe	7
Left lung	Upper lobe	1
	Lower lobe	5
Mediastinum		3
Pleural		2

The major lung resections were the main procedure, being performed for 18 patients. There 12 other procedures included mainly tumorectomy, wedge resection and biopsy.

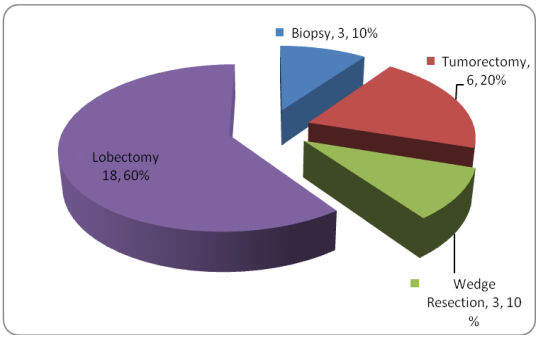

Figure 4. *Surgical Procedure*

Operative outcomes

Operation time

The operation time was calculated from skin incision until would closure. In some cases, the operation time also included the time for frozen histological examination. The mean duration of operation time for major lung resection, wedge resection, tumorectomy and biopsy were 243, 105, 80 and 58 minutes, respectively. The mean of intraoperative blood loss was 99.2ml for all procedures. The mean numbers of reload which were used for major lung resections, wedge resection, tumorectomy and biopsy were 4, 3, 0 and 0, respectively. The mean of the length incision were 3.24 ± 1.5cm (from 1 to 7cm).

Post-operative management

The chest tube was removed after 2.95 ± 0.2 days. The mean hospital stay was 4.79 ± 1.18 days for the whole group with no significant differences between each group.

Table 3. *Operative outcomes*

	Lobectomy	Wedge resection	Biopsy	Tumorectomy	P	
Operation time	243.57±98.08	105 ± 35.35	58.33 ± 20.2	80 ± 37.75	0.0035	183.4 ±113.8 (40-450)
Blood loss	129.4 ± 207.4	75 ± 35.4	30 ± 23.1	46.7 ± 47.3	0.0793	99.2 ± 170.2 (10-900)
Numbers of reload	4 ± 1.5	3	0	0		3.13 ± 1.98 (0-7)
Drainage time	2.92 ± 0.5		2.5 ± 0.6	3.5 ± 0.7		2.95 ± 0.62 (2-4)
Hospital stay	4.69 ± 1.2	4.5 ± 0.7	4.6 ± 1.3	5 ± 1	0.4393	4.79 ± 1.18 (4-7)
Length of incision						3.24 ± 1.5 (1-7)

Complications

There was one conversion to open surgery because of uncontrolled bleeding from pulmonary artery. No patient had postoperative outcomes and no 30 days mortality was recorded.

DISCUSSION

The evidence has shown the safety, feasibility and benefit of minimally invasive techniques in thoracic surgery due to creation of small incisions through on intercostal spaces without ribs spreading, results in less postoperative pain and fewer paraesthesias in addition to better cosmetic effects. Uniportal VATS is becoming accepted worldwide for minor and major procedures to treat thoracic and mediastinal pathologies[5,6]. The initial results are promising and the technical feasibility has been shown[6]. Some authors have reported using uniportal VATS approach in NSCLC in early stage and the results showed no significant differences between robotic surgery, VATS and open surgery[7,9]. Otherwise, the number of lymph node havested by VATS is not inferior in comparison with open surgery[8]. Moreover, VATS and robotic surgery described some benefits over open surgery such as shorter hospital stay and early post-operative recovery[10,11]. These benefits are achieved with equivalent oncological effectiveness. Also, it is reported that the advantages of uniportal approach are not confined only for the patients, but also for the surgeons. This technique provides a direct view of the target tissue. The parallel instrumentation achieved during the singleport approach mimics the maneuvers performed during open surgery[2,3,4]. In addition, the surgeon and the assistant are placed in front of the patient, so they have the same field of vision and the coordination is better[12].

The uniportal VATS was applied in out hospital since December 2016. We did modify the single incision to i- incision because we don't have wound retractor to cover the incisions. So we placed one more trocar above the main incision 1cm separately to keep the screen of scope clean. This also makes it possible to fix the thoracoscope in place and reduces the tendency to mutual interference of the instrument. This incision was used to place chest tube at the end of the operation.

In our study the mean operation time was 250 mins for lobectomy, which is longer than some authors[13] but we have similar intraoperative blood loss as well as postoperative outcomes to those reports by others[14]. We believe that with the accumulation of cases, this may be able to overcome. The limiting factor was using of disposable instruments for laparoscopy in VATS results in prolonging duration of operation. Specially designed uniportal VATS instruments with slight curvature and narrower shaft should be applied to allow for a smaller incision, reduced instrument fencing and optimized outcomes. Besides, without suitable reload for vessels, it was demanding for surgeon to input avoiding the possibility of damaging tissues around.

One patient had to be converted to open surgery due to uncontrolled bleeding from pulmonary artery. There was no morbidity or mortality reported in our study.

Despite Rodgers-Fischl PM et al[15] showed the average cost between thoracotomy and VATS did not vary significantly, the cost for VATS in our country, which not be covered by government insurance, is still a burden for patients.

Overall, the clinical outcomes of modified uniportal VATS in our hospital were similar to those of other studies therefore we consider them acceptable. However, as mentioned in a previous study[16], the uniportal VATS technique for major lung resection should be learned and performed carefully, especially during the initial period of the learning curve.

There are some limitations in our study, such as retrospective nature, the absence of evaluation of postoperative pain, paraestheris, short postoperative follow-up period or the lack data regarding survival and recurrence.

In conclusion, uniport VATS in our study is suggested to safe and feasible to perform. The procedure can be optimally learned and rigorous training is required for this technique. Furthermore, randomized controlled trials are necessary with more patients and additional long-term survival and especially oncological outcomes analyses should be conducted.

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CONCURRENT CHEMORADIOTHERAPY FOR ADVANCED STAGE LARYNGEAL CARCINOMA

BUI LE PHUOC THU THAO[1], DANG HUY QUOC THINH[1], LAM DUC HOANG[1], HUYNH CHI LONG[1]

ABSTRACT

Background:

Primary chemoradiotherapy is considered as a promised alternative option of treatment for patients with advanced laryngeal carcinoma because it can achieve high rate of organ preservation without sacrificing survival compared with radiation alone or conventional laryngectomy. Appropriate selection of patients for organ preservation approaches could enhance overall treatment outcome. We conduct a phase II organ preservation trial to determine the efficacy, feasibility, and toxicity of Concurrent Chemoradiotherapy (CCRT) for locally advanced laryngeal carcinoma.

Patients and Methods:

Laryngeal cancer patients had T3 squamous cell carcinoma of the larynx. These patients were technically total laryngectomy resectable. They were given one cycle of induction chemotherapy consisted cisplatin 100mg/m² on day 1 and fluorouracil 1000mg/m²/day for 4 days. Patients who achieved less than 50% response had immediate laryngectomy. Patients who achieved more than 50% response went on to CCRT with cisplatin 100mg/m² every 3 weeks for 3 cycles. Patients with residual disease after CCRT had planned salvage surgery.

Results:

Of 33 eligible patients, 28 patients (84.8%) achieved more than 50% response and received CCRT and 25 of them completed treatment. Among five patients (15.2%) whoachieved less than 50% response, only one agreed for total laryngectomy, 2 received CCRT and 2 received radiation alone. Of 25 patients with completion of treatment, 20 (80%) had completed response, and no patient had salvage surgery after chemoradiotherapy.

For acute toxicities: *Grade 3-4 toxicity in white blood cell, red blood cell and platelet seen in 12%, 8% and 4% patients. No patient developed grade 3 mucositis or dry mouth. Weight loss more than 10% was seen in 60% patients.*

The median follow-up time was 14 months. The overall survival rate at 1 year is 81.7%. Larynx preservation was achieved in 19/21 patients (90.5%).

Conclusion:

In patients with advanced laryngeal carcinoma, CCRT has high response rate and high larynx preservation rate with acceptable toxicities.

OBJECTIVE

The purpose of this study was:

- To determine the efficacy, feasibility, and toxicity of CCRT for locally advanced laryngeal carcinoma.

- To evaluate the functional preservation possibility of CCRT for locally advanced laryngeal carcinoma.

METHODS

Eligibility of patients

All patients have pathological confirmed, resectable, previous untreated, stage III or IV squamous cell carcinoma of the larynx. All patient were candidates for total laryngectomy.

From 2014 March to 2016 March, there were 33 eligible patients with T3 squamous cell carcinoma

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of the larynx. Endpoint were 2016 September or patient died.

Exclusion criteria: previous radiation treatment, compromised medical disease that unable to be afforded a whole course of CCRT.

Study Method

This is a case – series study

Induction chemotherapy

Cisplatin 100mg/m^2 was administered on day 1 and 5-fluorouracil 1000mg/m^2/d was administered as a 24-hour continuous infusion for 5 days.

Tumor assessment

All patient were examined by direct laryngoscopy before treatment and 3 weeks after induction chemotherapy to obtain bi-dimensional measurements for the primary tumor. The patient who classified as achieving a partial response (tumor regression was ≥50%) underwent CCRT. If not, they were indicated total laryngectomy.

Concurrent Chemoradiotherapy

Definite radiation began within 3 to 4 weeks after induction chemotherapy, total dose was 70Gy, 2Gy per fraction and 5 fractions a week. Cisplatin (100mg/m^2) was administered concomitantly on day 1, day 22 and day 43.

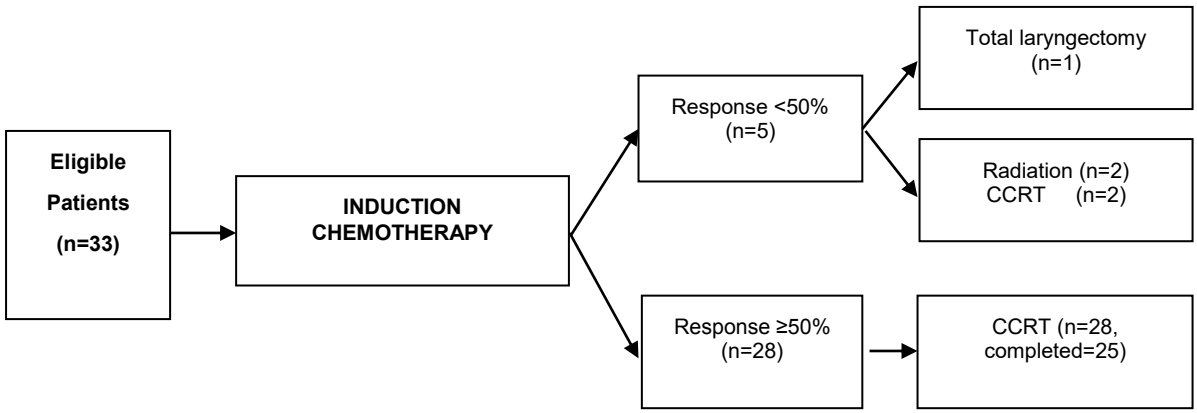
Criteria definitions

Respond evaluation based on RECIST 1.1.

Acute toxicities of Chemoradiation based on CTCAE v.4.0.

Voice - qualities assessment based on Voice - Handicap Index 10 (VHI-10).

RESULTS AND DISCUSSION



Patient characteristics

Between 2014 March to 2016 March there were 33 eligible patients were enrolled, most of the patients are male, only one patient was female. Table 1 lists the patients characteristics.

Table 1. *Patient Characteristics*

Characteristics	No. of patients	%
Male : Female	32:1	
Ages, years (mean)	58,3	
Stage III	19	57.6%
Stage IV	14	42.4%
Supraglottic	16	48.5%
Glottic	17	51.5%

Treatment characteristic

Feasibility and compliance of treatment: there were three patients (10.7%) were unable to complete the treatment regimen. Among patients who completed the radiation therapy, only 64% were able to received 3 cycles of chemotherapy. Delay of chemotherapy was common, seen in about 48% of patients.

The treatment characteristic is detailed in table 2.

Table 2. *Treatment Characteristics*

Characteristic	No. of patients	%
Not complete treatment	3/28	10,7
Complete 3 cycles of chemotherapy	16/25	64

Chemotherapy delay:	12/25	48
Poor performance status	8	32
Hematology toxicities	5	20
GI tract toxicities	8	32
Dermatitis radiation	1	4
Radiation delay	6/25	24

Treatment toxicities

During chemoradiotherapy, toxicities grade 3-4 were not common observed in this study. For instant, grade 3 of granulocytopenia was seen in 3 patients (12%) and grade 4 thrombocytopenia was seen in only one patients.

The toxicities of gastro-intestinal tract were more common. Most the patients experienced nausea, vomiting, mucositis and anorexia. Weight loss >5% seen in all the patients and 60% of them experienced weight loss >10%.

Table 3. *Chemoradiotherapy toxicities*

	% of Patients	
Toxicity	**Grade 3**	**Grade 4**
Granulocytopenia	12	0
Thrombocytopenia	0	4
Anemia	8	0
Mucositis	0	0
Anorexia	4	0
Dermatitis radiation	12	0
Weight loss >10%	60	

Response evaluation

All 33 patients received one cycle of induction chemotherapy, after which an endoscopic evaluation was planned. Twenty eight patients (85%) had more than 50% response at primary tumor and proceeded to definite CCRT. Five patients (15%) had less than 50% response but only one patient agreed for total laryngectomy.

Of 25 patients finished CCRT, 20 patients (80%) had completed response, and no patient had salvage surgery after chemoradiotherapy.

Table 4. *Primary tumor response after induction chemotherapy*

Authors	Chemotherapy regimen	No. of patients	%
Urba	Platinum + 5FU	97	75%
Worden	Platinum + 5FU	36	81%
Popovtzer	TPF	26	85%
This study	**Cisplatin + 5FU**	**33**	**85%**

Table 5. *Response to chemoradiotherapy*

Authors	Chemotherapy regimen	No. of patients	%
Patel	Cisplatin/ Carboplatin	21	76%
Semrau	Platinum + Paclitaxel	38	97%
Tung Ngo	Cisplatin weekly	49	55%
This study	**Cisplatin every 3 weeks**	**25**	**80%**

The median follow-up time was 14 months. The overall survival rate at 1 year is 81.7%. Larynx preservation was achieved in 19/21 patients (90.5%).

Larynx Preservation

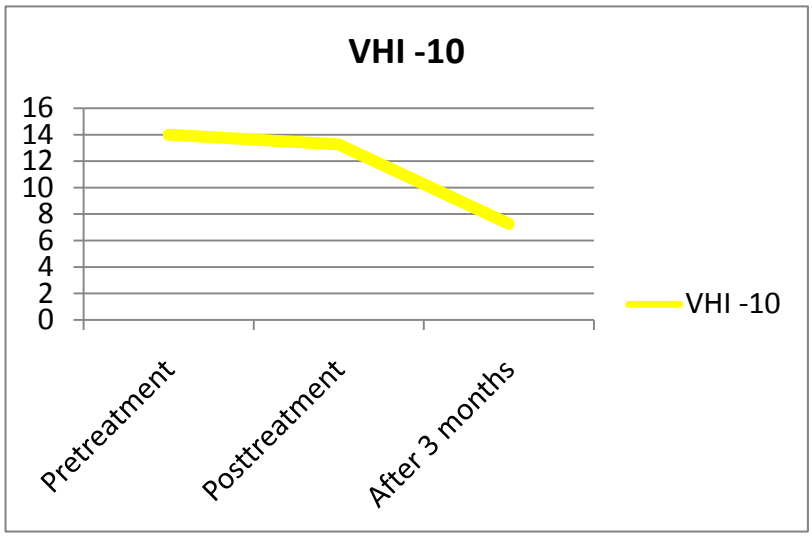
During treatment, two of the patients required feeding tubes and two required tracheostomy. One patient had progressive disease and need tracheostomy nine months after treatment.

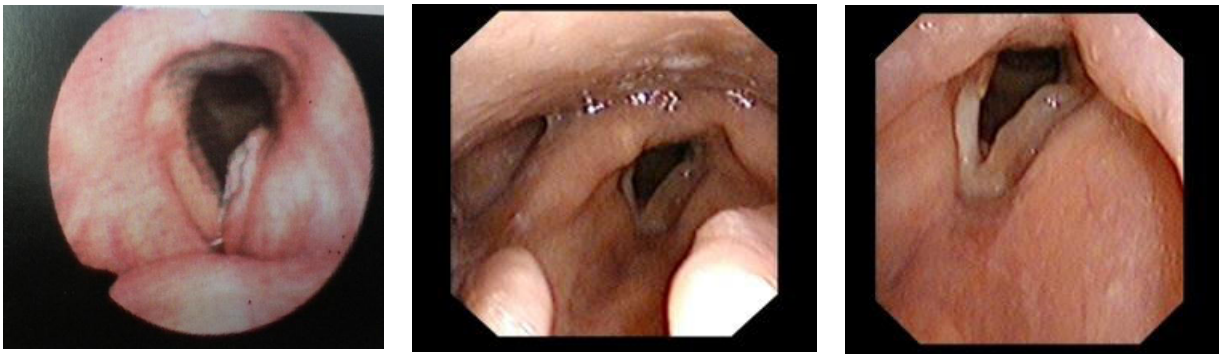
At the end of the study, there was no salvage laryngectomy indicated. In fact, after treatment, 4 patients experienced progressive disease, three of them died. The last one had lymph node progressive and not suitable for surgery.

Quality of Voice

VHI-10 was used to score the quality of voice of the patients before treatment (basement assessment), after treatment and 3 months later. Mean score for each assessment can be seen in figure 1. Although the quality of voice was not improve immediately after treatment, VHI-10 score was significantly smaller at 3 months after treatment compared to the basement assessment. Most the patients felt pleased with their voice.

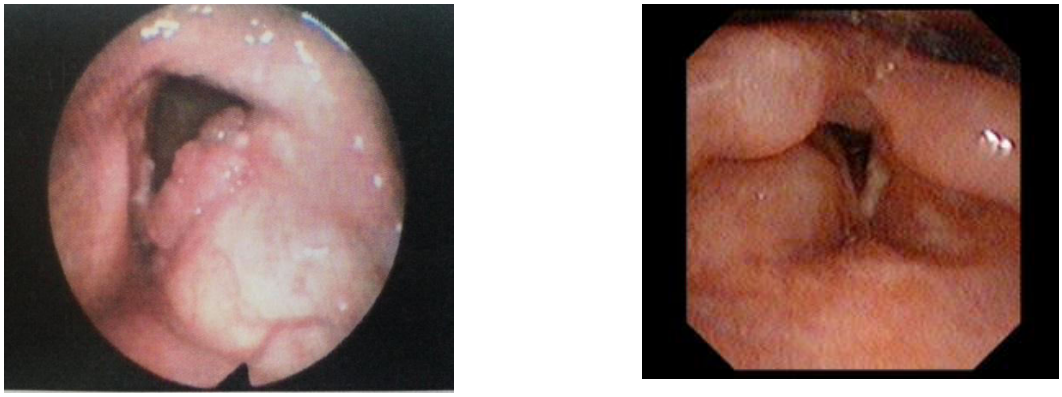
Figure 1. *Voice-Handicap index at different time of treatment course*





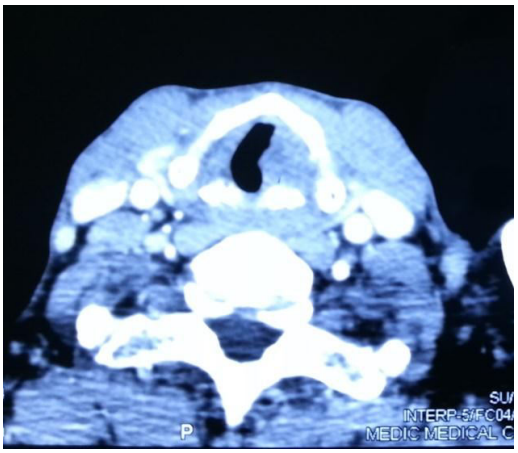
Before treatment **After induction chemo** **After CCRT**

ID 5492/14, male 47ys, stage III

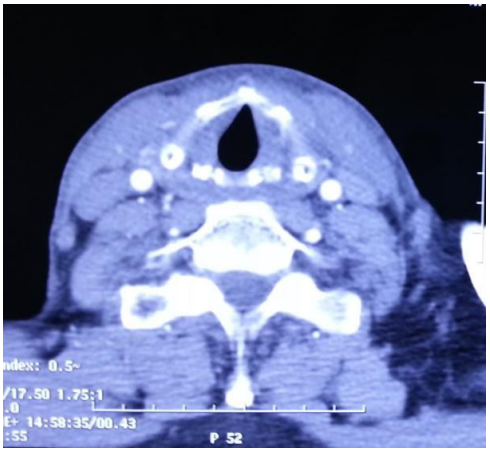


Before treatment **After chemoradiotherapy**

21862/15, male, 54 ys, stageIII



Before treatment



After treatment

ID 21770/14, male 70ys, stage III

CONCLUSION

The result of this study demonstrate that one cycle of induction chemotherapy identifies a group of patients who likely to be successfully treated with CCRT, achieving a high rate of larynx preservation and good function with acceptable toxicity.

With a short time of follow up, we realize that it is not possible to conclude a true survival advantage of the treatment. However, we are encouraged that the response rate to CCRT is promising with complete response seen in 80% patients. We believe this good response rate may be a result of the early selection from laryngectomy of patients likely to fail CCRT.

In summary, CCRT now is considered as an alternative option of treatment for patients with advanced laryngeal carcinoma. Induction chemotherapy should be considered as a strategy treatment to select patient for CCRT.

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