Fig. 3. Geographical distribution of cancer patients attending at National Institute of Cancer Research and Hospital (NICRH), Dhaka, Bangladesh during the period of 2008 to 2010.

Discussion

Using cancer registry data of 2,7281 patients at NICRH in Dhaka, Bangladesh we report increasing rate of cancer incidence over years. Higher rate of cancers among illiterate and aged people, lung cancer and breast cancer was the leading cancer among male and female, respectively.

Lack of adequate awareness about healthy life style and healthy diet is directly related with the literacy of a nation. Our findings that illiterate person had more cancer than others was in agreement with the study of Kachroo S & Etzel CJ[16]. Like other developing countries in Africa and Asia, Bangladesh also have low literacy rate[17], especially in the rural Bangladesh. Although

we could not report about cancer prevalence in rural Bangladesh, we believe, most of the cancers in rural areas are underreported because of lack of smooth access to health services for the rural people. Moreover, because of low level of awareness, people with cancer usually seek treatment from the traditional healers, including spiritual healers, homeopathy, unani and ayurveda. Most of these patients die without being recognized that they had cancers. Poverty adds additional fuel on this havoc.

We found the leading cancers in Bangladesh were the lung cancer in first rank followed by breast cancer and cervical cancer irrespective of sexes. Similar results were found from previous report[18] at NICRH in Bangladesh. However, two other studies reported lung cancer is the number two in rank among South Asian countries and other developing countries in the world[19, 20]. This might be due to the higher prevalence of smoking in Bangladesh than those studied countries. The use of smoked tobacco in Bangladesh was among males 44.7% and females 1.5%; and smokeless tobacco use among males 26.4% and females 27.9%[21, 22]. Smoking was considered as the single most preventable risk factor for lung cancer.

The risk of developing lung cancer increases with age[20] which supports our findings that highest cancer was among 45-54 year age group. It is because harmful toxic effects of unhealthy life style and diet accumulate as age increases leading to cancer among this age group. However, our findings that cancer declined steadily after this age group does not contradicts with the trend. Because, half of the cancer patients in Bangladesh die within five years of diagnosis, rate is low among extremely older population[13, 18]. Patients usually visit a cancer specialist at the very advanced stage fearing huge costs.

The present study found breast cancer as the leading cause of cancer among female in Bangladesh which was consisted with previously published report[18]. Some studies[19, 20] conducted in South Asia and other developing countries confirmed the breast cancer as 2nd or 3rd cancer among female. The high rate of breast cancer in Bangladesh might be due to several reasons, including lack of awareness about the benefit of breast self-examination (BSE) and early reporting to the doctor, poor compliance with follow-up for women with positive results, lack of education, lack of trust in the existing healthcare system and chances of getting cured for instances. However, certain cultural and religious practices were strongly influence the problem delay particularly among women. Discouraging about free communication between the sexes contributes their inhibition to show their disease. Moreover, even many women cannot comfortably discuss symptomatology involving the female organs with male physicians, their husbands or other women[23].

We also found cervical cancer as one of the most common (2nd) cancer among female in Bangladesh which was in line with some previously published studies[18-20]. Some studies[24] showed that 81% of cervical cancer cases occur in Latin America, Africa, Eastern/Southern Europe, Pacific Island Nations and South-central Asia. Moreover, cervical cancer was the leading cause of cancer related death among women in developing countries[25]. The major risk factors for cervical cancer were identified as Human papilloma virus (HPV), early sexual practice, multiple sexual partners, menstrual hygiene and unprotected sex[26-28]. Most of these risk factors are heavily prevailing among Bangladeshi population. Early sexual exposure was also identified as the risk factors for cervical cancer by a study done in Darjeeling, India[29].

The strength of our study was large number of cancer patients attending at NICRH. This is a tertiary level specialized hospital for cancer patient care and education of professionals. People from all corner of the country come to this hospital. Although patients have to bear or share cost for some of the treatment modalities, the treatment is given free in general. Therefore this hospital can attract patients from all socioeconomic strata for diagnostic, curative and palliative cares. Despite these facts, possibility of bias that people from around Dhaka city was included more in the cancer registry, so in our study, cannot be ruled out. Moreover, we could not consider patients who used to seek treatment from the private hospitals, from abroad or those who died at their residence.

In conclusion, an increasing trend of cancer was observed in Bangladesh. Lung and breast cancer was the leading cancer in male and female, respectively; and most frequent cancer was observed among illiterate and middle aged population. Whereas, cultural, religious, diet- and lifestyle-related issues are important in this context, we recommend exerting proper emphasis specifically on anti-tobacco campaign and breast self-examination for the females in addition to increasing overall awareness against cancers in Bangladesh.

Acknowledgements

This study was supported in part by a non-profit organization ECRIN (Epidemiology and Clinical Research Information Network) Kyoto, Japan.

Competing interests

The authors declare that they have no competing interests.

References

1) Stewart BW, Kleihues P, editors. World Cancer Report. Lyon: IARC Press; 2003.
2) Schottenfeld D, Beebe-Dimmer JL. Advances in cancer epidemiology: understanding causal mechanisms and the evidence for implementing interventions. *Annu Rev Public Health*, 2005; 26: 37-60.
3) Jemal A, Murray T, Samuels A, Ghafoor A, Ward E, Thun MJ. Cancer statistics, 2003. *CA Cancer J Clin*, 2003; 53: 5-26.
4) Ferlay J et al., editor. Globocan 2000. Cancer Incidence, Mortality

and Prevalence Worldwide. Lyon, France: IARC Cancer Base No. 5; 2001.
5) Jan S, Kimman M, Kingston D, Woodward M. The Socioeconomic Burden of Cancer in Member Countries of the Association of Southeast Asian Nations (ASEAN) - Stakeholder Meeting Report. *Asian Pac J Cancer Prev*, 2012; 13: 407-409.
6) Parkin DM. Global cancer statistics in the year 2000. *Lancet Oncol*, 2001; 2: 533-543.
7) Pisani P, Bray F, Parkin DM. Estimates of the world-wide prevalence of cancer for 25 sites in the adult population. *Int J Cancer*, 2002; 97: 72-81.
8) Faggiano F, Partanen T, Kogevinas M, Boffetta P. Socioeconomic differences in cancer incidence and mortality. *IARC Sci Publ*, 1997: 65-176.
9) Pisani P, Parkin DM, Munoz N, Ferlay J. Cancer and infection: estimates of the attributable fraction in 1990. *Cancer Epidemiol Biomarkers Prev*, 1997; 6: 387-400.
10) Ferlay J, Shin HR, Bray F, Forman D, Mathers C, Parkin DM. Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. *Int J Cancer*, 2010; 127: 2893-2917.
11) WHO. Cancer in the South-East Asia Region (SEA) Region - Quick facts. 2008 [cited 01 June 2012]; Available from: http://www.searo.who.int/en/section1174/section1459_16435.htm.
12) Banglapedia. National Encyclopedia of Bangladesh: Cancer. [cited 01 June 2012]; Available from: http://www.banglapedia.org/httpdocs/HT/C_0033.HTM.
13) Ministry of Health and Family Welfare. National cancer control strategy and plan of action 2009-15: Non Communicable Diseases and Other Public Health Interventions. Dhaka: Ministry of Health and Family Welfare; 2008 [cited 2012 25 May 2012]; Available from: http://openlibrary.org/books/OL23863848M/National_cancer_control_strategy_and_plan_of_action_2009-2015.
14) WHO. Cancer: Key facts. 2012 [cited 01 June 2012]; Available from: http://www.who.int/mediacentre/factsheets/fs297/en/.
15) Percy C, Fritz A, Jack A, Shanmugarathan S, Sobin L, Parkin DM, Whelan S. International Classification of Diseases for Oncology (ICD-O) 2000, World Health Organization.
16) Kachroo S, Etzel CJ. Decreasing the cancer burden in developing countries: concerns and recommendations. *Eur J Cancer Care (Engl)*, 2009; 18: 18-21.
17) UNDP-Human Development Reports. United Nations Development Plan (2007) Human and Income Poverty: Developing Countries-Adult Illiteracy Rate (% ages 15 and older). 2007 [cited 21 May 2012]; Available from: http://hdrstats.undp.org/indicators/20.html
18) WHO. Cancer Registry Report - National Institute of Cancer Research and Hospital 2005-2007. Dhaka: WHO; 2009 [cited 20 May 2012]; Available from: http://www.ban.searo.who.int/LinkFiles/Publication_Cancer_Registry_Report.pdf.
19) Boffetta P, Parkin DM. Cancer in developing countries. *CA Cancer J Clin*, 1994; 44: 81-90.
20) Moore MA, Ariyaratne Y, Badar F, Bhurgri Y, Datta K, Mathew A, Gangadharan P, Nandakumar A, Pradhananga KK, Talukder MH, Yeole BB, Sobue T. Cancer epidemiology in South Asia - past, present and future. *Asian Pac J Cancer Prev*, 2010; 11 Suppl 2: 49-66.
21) Centers for Disease Control and Prevention (CDC). Differences by sex in tobacco use and awareness of tobacco marketing -Bangladesh, Thailand, and Uruguay, 2009. *MMWR Morb Mortal Wkly Rep*, 2010; 59: 613-618.
22) Hanifi SM, Mahmood SS, Bhuiya A. Smoking has declined but not for all: findings from a study in a rural area of Bangladesh. *Asia Pac J Public Health*, 2011; 23: 662-671.
23) Lynch HT, Rahim MA. Cancer in the Third World: Bangladesh 1980. *Am J Public Health*, 1981; 71: 1158-1161.
24) Drain PK, Holmes KK, Hughes JP, Koutsky LA. Determinants of cervical cancer rates in developing countries. *Int J Cancer*, 2002; 100: 199-205.
25) Pisani P, Parkin DM, Bray F, Ferlay J. Erratum: Estimates of the worldwide mortality from 25 cancers in 1990. Int. J. Cancer, 83, 18-29 (1999). *Int J Cancer*, 1999; 83: 870-873.
26) de Silva R, Karunaratne K, Mendis LN, Ramesh R, Chow VT. PCR detection and typing of human papilloma virus DNA in squamous carcinoma of the cervix in a cohort of Sri Lankan women. *Ceylon Med J*, 2006; 51: 114-117.
27) Juneja A, Sehgal A, Mitra AB, Pandey A. A survey on risk factors associated with cervical cancer. *Indian J Cancer*, 2003; 40: 15-22.
28) Varghese C, Amma NS, Chitrathara K, Dhakad N, Rani P, Malathy L, Nair MK. Risk factors for cervical dysplasia in Kerala, India. *Bull World Health Organ*, 1999; 77: 281-283.
29) Bhattacharyya SK, Basu S, Banerjee S, Dastidar AG, Bagchi SR. An epidemiological survey of carcinoma cervix in north Bengal zone. *J Indian Med Assoc*, 2000; 98: 60-61, 66.

Int J Clin Oncol
DOI 10.1007/s10147-012-0382-z

ORIGINAL ARTICLE

Multicenter phase II study of modified FOLFOX6 as neoadjuvant chemotherapy for patients with unresectable liver-only metastases from colorectal cancer in Japan: ROOF study

Takao Takahashi · Yoshihisa Shibata · Yuichiro Tojima · Kenji Tsuboi · Eiji Sakamoto · Katsuyuki Kunieda · Hiroshi Matsuoka · Kazuyoshi Suzumura · Mikinori Sato · Tatsushi Naganuma · Junichi Sakamoto · Satoshi Morita · Ken Kondo

Received: 17 October 2011 / Accepted: 19 January 2012
© Japan Society of Clinical Oncology 2012

Abstract
Background Neoadjuvant chemotherapy for unresectable colorectal liver metastases can reduce tumor size, which sometimes leads to curative resection. The aim of the present study was to identify and describe patients with initially unresectable liver-only metastases from colorectal cancer who obtained sufficient chemotherapeutic benefit that eventually lead to the removal of the metastatic diseases in the liver.
Methods A phase II multicenter cooperative study was conducted in 38 medical institutions using modified FOLFOX6 (mFOLFOX6) as neoadjuvant chemotherapy from January 2008 to June 2009. Patients with liver-only metastases from colorectal cancer that was deemed not optimally resectable by liver surgeons received mFOLFOX6 as preoperative neoadjuvant chemotherapy for 6-8 cycles. Patients were reassessed for resectability after 6 cycles of mFOLFOX6. Surgery was carried out 3-6 weeks after chemotherapy. The primary endpoint was the rate of macroscopic curative surgery including liver resection.
Results 36 patients (23 male/13 female, ECOG performance status 0-1) were enrolled. The median age of the patients was 62.5 years; 78% (28 patients) had 5 or more metastatic tumors, and 50% (18 patients) had metastatic tumors over 5 cm diameter. The mFOLFOX6 regimen was

T. Takahashi (✉)
Department of Surgical Oncology, Gifu University School of Medicine, 1-1 Yanagido, Gifu 501-1194, Japan
e-mail: takaota@gifu-u.ac.jp

Y. Shibata
Department of Surgery, Toyohashi Municipal Hospital, Toyohashi, Japan

Y. Tojima
Department of Surgery, Chukyo Hospital, Nagoya, Japan

K. Tsuboi
Department of Surgery, Tosei General Hospital, Seto, Japan

E. Sakamoto
Department of Surgery, Nagoya Daini Red Cross Hospital, Nagoya, Japan

K. Kunieda
Department of Surgery, Gifu Prefectural General Medical Center, Gifu, Japan

H. Matsuoka
Department of Surgery, Fujita Health University, Toyoake, Japan

K. Suzumura
Department of Surgery, Aichi Medical University, Nagakute, Japan

M. Sato
Department of Gastroenterological Surgery, Nagoya City University Graduate School of Medical Sciences, Nagoya, Japan

T. Naganuma
Department of Surgery, Saiseikai Matsusaka General Hospital, Matsusaka, Japan

J. Sakamoto
Young Leaders' Program in Healthcare Administration, Department of Social Life Science, Nagoya University, Graduate School of Medicine, Nagoya, Japan

S. Morita
Department of Biostatistics and Epidemiology, Yokohama City University School of Medicine and University Medical Center, Yokohama, Japan

K. Kondo
Department of Surgery, Nagoya Medical Center, Nagoya, Japan

Published online: 02 March 2012

safety administered resulting in 18 partial responses (50%), 12 stable disease, and 4 progressive disease. There was no grade 3/4 neurotoxicity. Fourteen patients (38.9%) underwent surgery (R0: 13; R1: 1). Of these, thirteen patients (36.1%) underwent R0 surgery.

Conclusions Our data suggest that mFOLFOX6 has a high response rate in patients with liver-only metastases from colorectal cancer, allowing for R0 resection of liver metastases in a proportion of patients initially not judged to be optimally resectable.

Keywords ROOF study · mFOLFOX6 · Colorectal cancer · Unresectable liver-only metastases · Liver resection

Introduction

Colorectal cancer represents one of the most common cancers in Japan, and the liver is the most common site of metastases in patients with colorectal cancer. Liver metastases are a major cause of morbidity and mortality in this patient population. With the best supportive care, patients with liver metastases from colorectal cancer have a median survival time of 5–12 months [1–3]. Surgical resection of colorectal liver metastases is a potentially curative option, with a reported 5-year survival rate of 28–39% [4, 5]. However, about 80% of patients with colorectal liver metastases have unresectable diseases at the time of diagnosis, and long-term survival is not usually possible.

Historically, most of the patients with unresectable colorectal liver metastases have received palliative chemotherapy. However, a number of retrospective studies have reported the downsizing of colorectal liver metastases for rescue surgery following treatment with a combination of fluorouracil with irinotecan or with oxaliplatin, with the resection rate of 12.5–28% and 5-year survival rate of 33–50% after successful surgical resection [6, 7]. Resection of liver metastases can result in long-term survival in a subset of patients. A 5-year survival rate of 25–37% has been reported in a number of studies, with a median survival time of 24–42 months [8]. The improved efficacy of neoadjuvant chemotherapy has not only improved patient survival in a palliative setting, but has also offered a possibility of curative resection to previously unresectable patients with subsequent liver surgery after tumor downstaging by the chemotherapy. Adam et al. reported that liver resection could offer a possibility of long-term survival to patients with primarily unresectable metastases that were downstaged by chemotherapy. The survival rate was 33% at 5 years and 22% at 10 years, with a median survival of 39 months [5]. The use of neoadjuvant chemotherapy in patients with initially unresectable liver metastases has been explored in a prior study. Bismuth et al. [9] reported retrospectively on the potential for surgical resection in a group of patients receiving neoadjuvant chemotherapy with oxaliplatin, fluorouracil (5-FU), and leucovorin. The addition of oxaliplatin and irinotecan to 5FU in metastatic colorectal cancer (mCRC) has improved patient survival and the chance of downsizing initially unresectable mCRC, to allow curative-intent surgery. Albert et al. [10] reported a phase II study of FOLFOX4 in a group of patients with initially unresectable liver-only metastases from colorectal cancers through the North Central Center Treatment Group (NCCTG). Seventeen out of 42 patients (40%) underwent surgery after a median of 6 months of chemotherapy.

The aim of the present study was to identify and describe patients enrolled in this trial with initially unresectable liver-only metastases from colorectal cancer, who obtained sufficient chemotherapeutic benefit that eventually led to the removal of the metastatic diseases in the liver. This study was a phase II clinical trial of mFOLFOX6 in a group of patients with initially unresectable liver-only metastases from colorectal cancer. The primary endpoint of this study was to evaluate the resection rate of the patients who had been diagnosed with unresectable colorectal cancer metastasis, who turned out to be resectable after treatment with mFOLFOX6. Secondary endpoints included (1) R0 resection rate, (2) overall survival, (3) response rate to neoadjuvant chemotherapy, (4) percentage reduction of the tumor size after chemotherapy, (5) pathological response rate, (6) adverse event of neoadjuvant chemotherapy, (7) liver damage after mFOLFOX6 treatment and safety of hepatectomy after mFOLFOX6 neoadjuvant chemotherapy.

Patients and methods

Patient selection

Patients with liver-only metastases from colorectal cancer deemed unresectable by surgeons who were experienced in liver surgery were considered as potential candidates for the study. Unresectable liver metastases was defined as (1) $\geq$5 metastatic tumors and/or (2) a tumor >5 cm in maximum diameter or technically unresectable (inadequate future liver remnant even after surgery), such as tumors adjacent to major vascular structures that would preclude resection with tumor-free margins. At the time of study entry, patients were required to have imaging of the liver with computed tomography or magnetic resonance imaging, no evidence of extrahepatic disease and no previous history of chemotherapy with oxaliplatin or irinotecan. To

be eligible for enrolment, patients had to be aged between 20 and 75 years old, have histologically proven mCRC, adequate organ function (AST, ALT $\leq 3\times$ upper limit of normal, bilirubin $\leq 2\times$ upper limit of normal, and creatinine ≤ 1.2 mg/dl), adequate bone marrow function, and an Eastern Cooperative Oncology Group performance status of 0–1. Patients were excluded from study entry if they had received prior therapy such as hepatectomy, radiotherapy, or MCT/RFA for liver metastases. A signed written informed consent was obtained from all patients before initiating therapy. Women who were pregnant or breast-feeding were also excluded from participation to the study. This trial was approved by the medical ethics committees of all participating institutions.

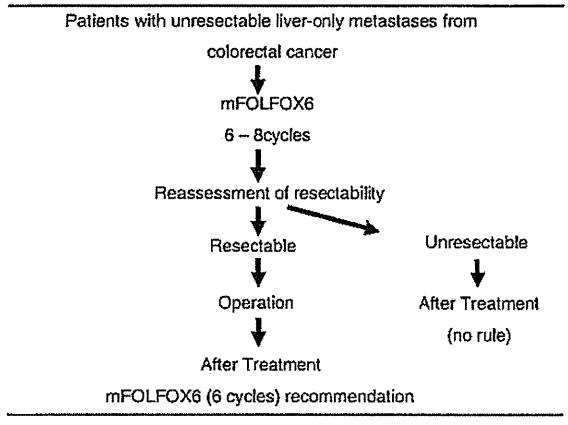
Neoadjuvant chemotherapy

Patients received mFOLFOX6, which consisted of biweekly oxaliplatin 85 mg/m^2, followed sequentially by leucovorin 400 mg/m^2, bolus 5FU 400 mg/m^2, and then continuous-infusion 5FU 2400 mg/m^2 over 46 h for 6–8 cycles.

Disease evaluation

Table 1 shows the profile of the Resection of metastatic colorectal cancer after Oxaliplatin, Fluorouracil, and leucovorin (ROOF) study. Patients with unresectable liver-only metastases from colorectal cancer were treated with 6–8 cycles of mFOLFOX6 as neoadjuvant chemotherapy. Tumor response was assessed every three cycles (6 weeks) with the same method as baseline, and was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Treatment was planned for 6–8 cycles.

Table 1 The outline of the ROOF study of patients with unresectable liver-only metastases from colorectal cancer



Reassessments for resectability after neoadjuvant chemotherapy were made. Hepatic resection was attempted by investigators when technically positive and when potentially curative. If it was judged that the tumor turned out to be resectablewhen it had initially been determined unresectable, tumor resection was planned within 3–6 weeks from the last administration of preoperative chemotherapy. Six cycles of mFOLFOX6 as adjuvant postoperative chemotherapy is recommended after hepatectomy.

Endpoints

The primary endpoint was the rate of patients with macroscopically curative surgery including liver resection. The definition of the patients who completed the treatment was those with unresectable liver-only metastases from colorectal cancer who were able to be treated with 6–8 cycles of mFOLFOX6 as neoadjuvant chemotherapy, with macroscopic R0 hepatectomy performed within 3–6 weeks of the last treatment cycles. If the excision of all the metastases was not possible, it was assumed that RFA or MCT in addition to hepatectomy was acceptable as the complete treatment.

Secondary endpoints included R0 resection rate, overall survival, response rate of neoadjuvant chemotherapy, percentage reduction after chemotherapy, pathological response rate, adverse event of neoadjuvant chemotherapy, and liver damage after mFOLFOX6 treatment and safety of hepatectomy.

Statistical considerations

The sample size was calculated to be 32 in order to show an improvement in resection rate from 20 to 40% with the acceptance of a 5% type I error under a 80% statistical power. Taking ineligible patients into account, the sample size in this study was set at 35.

Results

Patients characteristics

A phase II multicenter cooperative study was conducted in 38 medical institutions using mFOLFOX6 as neoadjuvant chemotherapy from January 2008 to June 2009. 36 patients (23M/13F, ECOG PS 0-1) were enrolled. Eligible patient characteristics at the time of study entry are listed in Table 2. The median age of the patients was 62.5 years, 78% (28 patients) had 5 or more metastatic tumors, and 56% (20 patients) had metastatic tumors over 5 cm in diameter. In these cases, 15 patients (42%) had ≥ 5

metastatic tumors and at least one tumor >5 cm in maximum diameter (H3) [11]. Moreover, 3 cases with liver metastases that were technically unresectable, with <5 metastatic tumors and a tumor <5 cm in maximum diameter (H1) [11], were noted (Table 2). H1, H2, and H3 of liver metastases are defined as in General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus: 7th Edition, 2009, by Japanese Society for Cancer of the Colon and Rectum [11]. The synchronicity of liver metastases was 32 synchronous (89%) and 4 metachronous (11%).

Neoadjuvant treatment administration and adverse events

Thirty-one patients (86.1%) out of 36 enrolled patients completed treatment with 6–8 cycles of mFOLFOX6, with a median of 6 cycles of treatment (range 1–8 cycles).

For safety assessment, adverse events were graded according to National Cancer Institute Common Criteria version 2.0. With regard to the hematological toxicity, neutropenia was observed as grade 3 in 8 patients, and grade 4 in 3 patients (Table 3). As for non-hematological toxicity, there were 4 patients with grade 2 peripheral neuropathy. Grade 3/4 adverse events included nausea, vomiting, and stomatitis; there was one case (3%) with grade 3 (Table 3). No patient died from the mFOLFOX6 treatment. Six to eight cycles of mFOLFOX6 as neoadjuvant chemotherapy were administered safely in general.

Table 2 Patient characteristics

Characteristic	Cases	%
Age (years), median (range)	62.5 (45–72)	
Sex		
Male	23	64
Female	13	36
ECOG		
PS 0	35	97
PS 1	1	3
Primary tumour site		
Colon	18	50
Rectum	18	50
Reason for unresectability		
≥5 metastases	28	78
>5 cm	20	56
Technically non-resectable	3	8
Before treatment		
Operation	28	78
No operation	8	22
Synchronicity of liver metastases		
Synchronous	32	89
Metachronous	4	11

There was only one case (7%) of perioperative complications, with MRSA infection, among 14 hepatectomies.

Best response of neoadjuvant chemotherapy

The mFOLFOX6 regimen was safety administered, resulting in 18 partial responses (50%), 12 stable disease, and 4 progressive disease (Table 4). A high disease control rate of 83.3% (30/36) was also confirmed by this study.

Resection rate

14 out of 36 patients (38.9%) underwent surgery with curative intent, in whom R0 resection was achieved in 13 out of 14 patients (R0: 13; R1: 1). Thirteen patients (36.1%) underwent R0 surgery after all. Of 36 patients enrolled with unresectable liver-only metastases from colorectal cancer, the number of patients who could be treated with 6–8 cycles of mFOLFOX6 treatment was 31 (86.1%). Five cases dropped out from the treatment in 1–5

Table 3 Toxicity

No. of patients ($n = 36$)					
NCI-CTC grade:	1	2	3	4	3/4 (%)
Hematotoxicity					
Leukopenia	7	9	3	0	8
Neutropenia	2	4	8	3	31
Thrombopenia	20	5	0	0	0
Anemia	19	7	1	0	3
Non-hematotoxicity					
Peripheral neuropathy	16	4	0	0	0
Nausea	9	4	1	0	3
Vomiting	1	0	1	0	3
Diarrhea	4	1	0	0	0
Appetite loss	4	0	0	0	0
Fatigue	2	0	0	0	0
Fever	2	1	0	0	0
Stomatitis	3	2	1	0	3
Dysgeusia	3	1	0	0	0

Table 4 Best response to neoadjuvant chemotherapy

	Cases ($n = 36$)	%
Complete response	0	0
Partial response	18	50.0
Stable disease	12	33.3
Progressive disease	4	11.1
Not evaluable	2	5.6

cycles, although it was a study protocol that six cycles or more of chemotherapy were received. Those cases with poor compliance were not able to undergo hepatectomy.

Characteristics of patients undergoing hepatectomy

Fourteen patients (11 male/3 female, ECOG performance status 0) underwent attempted post-chemotherapeutic resection of liver-only unresectable metastases from colorectal cancer. Theedian age of the patients was 65.2 years; the synchronicity of liver metastases were 11 synchronous and 3 metachronous. H1, H2, and H3 degrees of liver metastases occurred in one case, 10 cases, and 3 cases, respectively [11]. The median number of cycles of neoadjuvant chemotherapy was 6.5.

There were 9 cases who underwent hepatectomy among 15 cases who had received six cycles of mFOLFOX6. All 3 cases who received seven cycles of mFOLFOX6 underwent hepatectomy. However, there were only 2 cases who became eligible for hepatectomy among 12 cases who had received up to eight cycles of mFOLFOX6. According to the protocol treatment of 8 cycles of mFOLFOX6, only one case was able to undergo hepatectomy after additional mFOLFOX6. Though the standard in the protocol by which the operation is performed was after 3 weeks and within 6 weeks from the final chemotherapy, there were four cases (29%) who actually underwent hepatectomy after 7 weeks due to convenience for the patient and the hospital or problems with liver function.

Surgical procedures were partial hepatectomy in 3 patients, hepatic segmentectomy in 2 patients, hepatic lobectomy in 2 patients, hepatic segmentectomy plus partial hepatectomy in 2 patients, hepatic lobectomy plus partial hepatectomy in 2 patients, hepatic extended lobectomy plus partial hepatectomy in 2 patients, and one hepatectomy including RFA.

Degree of liver metastasis (H factor)

General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus: 7th Edition, 2009, by Japanese Society for Cancer of the Colon and Rectum indicates an H factor regarding liver metastases [11]. H1 is defined as less than 4 liver metastases and below 5 cm in maximum diameter of liver metastases. On the other hand, H3 is defined as more than 5 liver metastases and over 5 cm in maximum diameter of liver metastases. H2 is defined as anything except H1 and H3. The response rates of H1, H2, and H3 were 66.7% (2 out of 3 H1 cases), 55.6% (10 out of 18 H2 cases), and 40.0% (6 out of 15 H3 cases), respectively. In all cases, the response rate was relatively high. There was no significant difference in response rate according to the H factor. There was only one case (33.3%) who underwent hepatectomy among the three H1 cases of patients who could not technically have liver metastases resected. There were ten cases (55.6%) who underwent hepatectomy among 18 H2 cases with marginally unresectable liver metastases. There were three cases (20.0%) who underwent hepatectomy among 15 H3cases. The rate of hepatectomy was the highest in H2. We were able to perform hepatectomy in one H1 case out of two with successful chemotherapy, and in seven H2 cases out of ten with successfulchemotherapy. Even though there were six H3 cases with successfulchemotherapy, we could perform hepatectomy in only one case. In other word, it is difficult to perform hepatectomy even if chemotherapy is successful in H3 cases.

Discussion

Colorectal cancer is the third leading cause of cancer death, primarily attributed to metastatic disease rather than to the primary tumor in Japan. Surgery remains the only potentially curative treatment for metastatic disease. Less than 15% of patients with metastatic involvement are candidates for surgery. Some studies have continued to report good overall survival for patients undergoing surgical resection of their liver-only metastases from colorectal cancer [4, 12]. Chemotherapy as a first-line treatment for metastatic colorectal cancer has greatly improved within the last decade. In recent years, the survival of patients with advanced colorectal cancer has been improved, initially by the use of oxaliplatin- or irinotecan-based combination chemotherapy. Subsequently, it has been shown that the efficacy of cytotoxic chemotherapy can be enhanced by the addition of novel targeted agents, notably the anti-vascular endothelial growth factor (VEGF) monoclonal antibody bevacizumab and the anti-epidermal growth factor receptor (EGFR) monoclonal antibody cetuximab.

Chemotherapeutic agents developed in colorectal cancer treatment, such as oxaliplatin associated with 5FU/LV, have demonstrated the ability to reduce tumor burden such that an important fraction of patients initially judged to be inoperable can be resected with curative intent [5, 12]. Delaunoit et al. [13] reported that post-chemotherapy surgical management of advanced colorectal cancer resulted in a 4.1% metastatic disease resection rate, and resection of metastatic disease after chemotherapy is possible in a small but important subset of patients with metastatic colorectal cancers, particularly after receiving an oxaliplatin-based chemotherapy regimen, with encouraging overall survival and time to progression observed in these highly selected patients. Tournigand et al. [14] found similar results for the secondary surgery rate in their trial, with a significant difference between patients treated with FOLFOX6 and

FOLFIRI (22 vs. 9%, $P = 0.02$). Response rate and resection rate is better for oxaliplatin-based chemotherapy such as FOLFOX. The resection rate has also been prospectively evaluated within phase II and III trials in patients with any-site mCRC, with relative risk of 33–66% and R0 resection rates of up to 22% reported, despite the unselected population [13–19] (Table 5).

Recently, an increasing number of reports on liver resection following intensive chemotherapy in patients with initially unresectable liver metastases have been published (Table 5). Prospective evaluation of conversion chemotherapy for the patients with liver-only, primarily unresectable disease has been undertaken in the phase II setting, with response rates of 48–71% and R0 resection rate of 12–40% in these selected populations [9, 10, 12, 15, 17, 20]. Alberts et al. [10] reported that twenty-five patients (60%) had tumor reduction and seventeen patients (40%) underwent surgery after a median of 6 months of FOLFOX4 chemotherapy in colorectal cancer patients with unresectable liver-only metastases (A North Central Cancer Treatment Group Phase II Study), which is consistent with other studies assessing the activity of FOLFOX4 as first-line therapy for liver-limited metastatic colorectal cancer [13]. The median overall survival from mCRC treated with 5-FU, oxaliplatin and irinotecan has reached over 20 months, whether given concomitantly [15] or sequentially [14], but, despite this, <5% of unresectable patients will live as long as 5 years with chemotherapy alone. In contrast, the reported 5-year survival rate of the highly selected group of patients with initial unresectable liver-only disease treated with conversion chemotherapy, then surgery, ranges from 33 to 50% [5, 6, 20, 21].

In retrospective analysis, a direct correlation between tumor response rate and resection rate has been shown in studies investigating patients with unresectable colorectal liver metastases [21]. A superior response rate has been reported with the FOLFOXIRI regimen (66 vs. 41% with FOLFIRI) which is not able to be used in the first-line setting, with a corresponding increase in R0 resection rate, reported as 36% in a subgroup of patients with liver-only metastatic disease [15]. An apparent increase in steatohepatitis and subsequently increased 90-day mortality after

Table 5 Post-chemotherapy surgical management of advanced colorectal cancer

Authors	Trial	Metastases	Regimen	*n*	Resectability rate (%)
Delaunoit et al. [13]	N9741		FOLFOX4	267	4.1
Tournigand et al. [14]	GERCOR		FOLFOX6	111	22
Tournigand et al. [14]	GERCOR		FOLFIRI	109	9.0
Falcone et al. [15]	GONO		FOLFOXIRI	122	15
Falcone et al. [15]	GONO		FOLFIRI	122	6
de Gramont et al. [16]			FOLFOX4	210	6.7
Okines et al. [17]	First BEAT		Oxaliplatin-based chemotherapy	949	16.1
Okines et al. [17]	First BEAT		Irinotecan-based chemotherapy	662	9.7
Okines et al. [17]	NO16966		FOLFOX4/XELOX + bevacizumab	699	8.4
Okines et al. [17]	NO16966		FOLFOX4/XELOX	701	6.1
Van Cutsem et al. [18]	CRYSTAL		FOLFIRI + cetuximab	599	7.0
Van Cutsem et al. [18]	CRYSTAL		FOLFIRI	599	3.7
Bokemeyer et al. [19]	OPUS		FOLFOX6 + cetuximab	169	9.8
Bokemeyer et al. [19]	OPUS		FOLFOX4	168	4.1
Bismuth et al. [9]		Liver-only metastases	Oxaliplatin-based chemotherapy	330	16
Alberts et al. [10]	NCCTG	Liver-only metastases	FOLFOX4	44	40
Adam et al. [12]		Liver-only metastases	Oxaliplatin-based chemotherapy	701	13.5
Falcone et al. [15]	GONO	Liver-only metastases	FOLFOXIRI	39	36
Falcone et al. [15]	GONO	Liver-only metastases	FOLFIRI	42	12
Okines et al. [17]	First BEAT	Liver-only metastases	Oxaliplatin-based chemotherapy	350	24.3
Okines et al. [17]	First BEAT	Liver-only metastases	Irinotecan-based chemotherapy	230	18.7
Okines et al. [17]	NO16966	Liver-only metastases	FOLFOX4/XELOX + bevacizumab	211	12.3
Okines et al. [17]	NO16966	Liver-only metastases	FOLFOX4/XELOX	207	11.8
Folprecht et al. [20]	CELIM	Liver-only metastases	FOLFOX6 + cetuximab	53	38
Folprecht et al. [20]	CELIM	Liver-only metastases	FOLFIRI + cetuximab	53	30
Our paper	ROOF	Liver-only metastases	mFOLFOX6	36	38.9

liver resection has been reported with irinotecan given before liver surgery. Oxaliplatin is also known to affect the liver, causing sinusoidal dilatation in 19% of cases in the same series [22]. It is interesting to note that in a retrospective series of 105 patients treated with oxaliplatin-based chemotherapy with or without bevacizumab, the investigators reported a lower incidence and severity of sinusoidal dilatation in patients receiving bevacizumab ($P < 0.01$) [23]. Although the choice of chemotherapy regimen may be a key to maximizing resection rate with bevacizumab combinations, the choice to be made is unclear [17].

There are fewer safety concerns with the addition of the EGFR monoclonal antibody, cetuximab, to neoadjuvant chemotherapy. The CELIM study compared two treatment arms both containing cetuximab combined with FOLFIRI or FOLFOX6. After eight cycles, in technically unresectable disease, treatment was continued for four further cycles. In that study, the response rates of FOLFIRI plus cetuximab and FOLFOX6 plus cetuximab reached 57 and 68%, respectively. R0 resection rates of FOLFIRI plus cetuximab and FOLFOX6 plus cetuximab were 30 and 38%, respectively [20].

In our prospective study, we evaluated the efficacy of a combination regimen, 6–8 cycles of mFOLFOX6, in the neoadjuvant treatment of patients with unresectable liver metastases. The present study confirmed the well-known efficacy of mFOLFOX6, with a relatively high response rate of 50% and R0 resection rate of 36.1%. Our data indicate that neoadjuvant chemotherapy is effective mainly for patients with H2, which is defined as more than 5 liver metastases or over 5 cm in maximum diameter of liver metastases considered suitable for surgery after neoadjuvant chemotherapy. The crucial endpoint of neoadjuvant treatment is the achievement of a high R0 resection rate. Strategies that result in higher response rates can lead to high R0 rates.

The optimal regimen for patients with potentially resectable diseases is yet to be defined, but a strong correlation between response to chemotherapy and subsequent resection rate has been described [6]. Therefore, the goal of current medical treatment for unresectable metastatic colorectal cancer is to improve tumor response to maximize the rates of potentially curative resection. As mentioned above, randomized studies have recently shown that the addition of cetuximab to first-line chemotherapy (FOLFOX or FOLFIRI) significantly improves efficacy in patients without activating mutations of the *KRAS* gene in their tumors [18–20]. The use of novel agents such as cetuximab may also provide additional benefit for the R0 resection rate of colorectal liver metastases. Further studies need to address the optimum neoadjuvant combination treatment for patients with initially unresectable liver metastases and standardized criteria for determining respectability. Finally, we suggest that mFOLFOX6 has a high response rate in patients with liver-only metastases from colorectal cancer, allowing for R0 resection of liver metastases in a proportion of patients initially not judged to be optimally resectable.

Acknowledgments We thank Mai Hatta for her great help. This work was supported, in part, by a Non Profit Organization Epidemiological & Clinical Research Information Network (ECRIN).

Conflict of interest No author has any conflict of interest.

References

1. Finan PJ, Marshall RJ, Cooper EH et al (1985) Factors affecting survival in patients presenting with synchronous hepatic metastases from colorectal cancer: a clinical and computer analysis. Br J Surg 72:373–377
2. Goslin R, Steele G, Zamcheck N et al (1982) Factors influencing survival in patients with hepatic metastases from adenocarcinoma of the colon or rectum. Dis Colon Rectum 25:749–754
3. Bengtsson G, Carlsson G, Hafström L et al (1981) Natural history of patients with untreated liver metastases from colorectal cancer. Am J Surg 141:586–589
4. Fong Y, Fortner J, Sun RL et al (1999) Clinical score for predicting recurrence after hepatic resection for metastatic colorectal cancer: analysis of 1001 consecutive cases. Ann Surg 230:309–318
5. Adam R, Delvart V, Pascal G et al (2004) Rescue surgery for unresectable colorectal liver metastases downstaged by chemotherapy: a model to predict long-term survival. Ann Surg 240:644–657
6. Adam R, Wicherts DA, de Haas RJ et al (2009) Patients with initially unresectable colorectal liver metastases: is there a possibility of cure? J Clin Oncol 27:1829–1835
7. Simmonds PC, Primrose JN, Colquitt JL et al (2006) Surgical resection of hepatic metastases from colorectal cancer: a systematic review of published studies. Br J Cancer 94:982–999
8. Fong Y (1999) Surgical therapy of hepatic colorectal metastasis. CA Cancer J Clin 49:231–255
9. Bismuth H, Adam R, Lëvi F et al (1996) Resection of nonresectable liver metastases from colorectal cancer after neoadjuvant chemotherapy. Ann Surg 224:509–520
10. Alberts SR, Horvath WL, Sternfeld WC et al (2005) Oxaliplatin, fluorouracil, and leucovorin for patients with unresectable liver-only metastases from colorectal cancer: a North Central Cancer Treatment Group Phase II Study. J Clin Oncol 23:9243–9249
11. General Rules for Clinical and Pathological Studies on Cancer of the Colon, Rectum and Anus: 7th Edition, 2009: Japanese Society for Cancer of the Colon and Rectum
12. Adam R, Avisar E, Ariche A et al (2001) Five-year survival following hepatic resection after neoadjuvant therapy for nonresectable colorectal. Ann Surg Oncol 8:347–353
13. Delaunoit T, Alberts SR, Sargent DJ et al (2005) Chemotherapy permits resection of metastatic colorectal cancer: experience from Intergroup N9741. Ann Oncol 16:425–429
14. Tournigand C, André T, Achille E et al (2004) FOLFIRI followed by FOLFOX6 or the reverse sequence in advanced colorectal cancer: a randomized GERCOR study. J Clin Oncol 15:229–237
15. Falcon A, Ricci S, Brunetti I et al (2007) Phase III trial of infusional fluorouracil, leucovorin, oxaliplatin, and irinotecan (FOLFOXIRI) compared with infusional fluorouracil, leucovorin,

and irinotecan (FOLFIRI) as first-line treatment for metastatic colorectal cancer: the Gruppo Oncologico Nord Ovest. J Clin Oncol 25:1670–1676
16. de Gramont A, Figer A, Seymour M et al (2000) Leucovorin and fluorouracil with or without oxaliplatin as first-line treatment in advanced colorectal cancer. J Clin Oncol 18:2938–2947
17. Okines A, del Puerto O, Cunningham D et al (2009) Surgery with curative-intent in patients treated with first-line chemotherapy plus bevacizumab for metastatic colorectal cancer First BEAT and the randomised phase-III NO 16966 trial. Br J Cancer 101:1033–1038
18. Van Cutsem E, Köhne CH, Hitre E et al (2009) Cetuximab and chemotherapy as initial treatment for metastatic colorectal cancer. N Engl J Med 360:1408–1417
19. Bokemeyer C, Bondarenko I, Makhson A et al (2009) Fluorouracil, leucovorin, and oxaliplatin with and without cetuximab in the first-line treatment of metastatic colorectal cancer. J Clin Oncol 27:663–671
20. Folprecht G, Gruenberger T, Bechstein WO et al (2010) Tumour response and secondary respectability of colorectal liver metastases following neoadjuvant chemotherapy with cetuximab: the CELIM randomized phase 2 trial. Lancet Oncol 11:38–47
21. Folprecht G, Grothey A, Albert S et al (2005) Neoadjuvant treatment of unresectable colorectal liver metastases: correlation between tumor response and resection rates. Ann Oncol 16:1311–1319
22. Vauthey JN, Pawlik TM, Ribero D et al (2006) Chemotherapy regimen predicts steatohepatitis and an increase in 90-day mortality after surgery for hepatic colorectal metastases. J Clin Oncol 24:2065–2072
23. Ribero D, Wang H, Donadon M et al (2007) Bevacizumab improves pathologic response and protects against hepatic injury in patients treated with oxaliplatin-based chemotherapy for colorectal liver metastasis. Cancer 110:2761–2767

Asia-Pacific Journal of Public Health
http://aph.sagepub.com/

Trends and Barriers to HIV Testing Among Tuberculosis Patients in Prey Kabas Operational District, Takeo Province, Cambodia

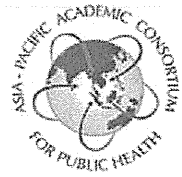
Wannak Samrith, Mahbubur Rahman, Md. Harun-Or-Rashid and Junichi Sakamoto

Asia Pac J Public Health published online 16 May 2012
DOI: 10.1177/1010539512445190

The online version of this article can be found at:
http://aph.sagepub.com/content/early/2012/05/03/1010539512445190

Published by:
SAGE
http://www.sagepublications.com

On behalf of:



Asia-Pacific Academic Consortium for Public Health

Additional services and information for *Asia-Pacific Journal of Public Health* can be found at:

Email Alerts: http://aph.sagepub.com/cgi/alerts

Subscriptions: http://aph.sagepub.com/subscriptions

Reprints: http://www.sagepub.com/journalsReprints.nav

Permissions: http://www.sagepub.com/journalsPermissions.nav

>> OnlineFirst Version of Record - May 16, 2012

What is This?

Downloaded from aph.sagepub.com at NAGOYA UNIVERSITY MEDICAL LIBRARY on July 24, 2012

Asia-Pacific Journal of Public Health
XX(X) 1–9
© 2012 APJPH
Reprints and permission:
sagepub.com/journalsPermissions.nav
DOI: 10.1177/1010539512445190
http://aph.sagepub.com
SAGE

Trends and Barriers to HIV Testing Among Tuberculosis Patients in Prey Kabas Operational District, Takeo Province, Cambodia

Wannak Samrith, MD[1,2], Mahbubur Rahman, MD, PhD[3], Md. Harun-Or-Rashid, MBBS, MS[1], and Junichi Sakamoto, MD, PhD, FACS[1]

Abstract

Data for this study were obtained from 2375 tuberculosis (TB) patients registered during 2007-2009 and 43 health providers to examine the trend of TB patient referral for HIV (human immunodeficiency virus) testing and to investigate provider-associated barriers to the referral in Prey Kabas operational district, Takeo province, Cambodia. Referral rate for HIV testing was 4.4% (30/684) in 2007, 15.4% (116/751) in 2008, and 30.1% (283/940) in 2009, with a significant upward trend over the period of time ($P = .009$). The main barriers perceived by health providers were poor knowledge about TB/HIV, lack of communication skills, absence of any target plan for TB patient referral for HIV testing, and fear associated with informing positive test results to the TB patients and the associated stigma. Strategies to raise awareness about HIV/AIDS/TB among TB patients and their providers may improve the current state of low referral and its barriers in Cambodia.

Keywords

Cambodia, HIV, operational district, referral, tuberculosis

Introduction

Tuberculosis (TB) is the leading cause of death in adults infected with human immunodeficiency virus (HIV).[1,2] Death occurs in up to 50% of these patients, usually within 2 months after TB has been diagnosed.[3-7] In 2004, the World Health Organization (WHO) recommended that all TB patients be referred for HIV testing and all people living with HIV/AIDS be screened for TB in countries with HIV prevalence ≥1% in adults and ≥5% in TB patients.[8] In an attempt to

[1]Nagoya University Graduate School of Medicine, Nagoya, Japan
[2]Ministry of Health, Takhmao Town, Cambodia
[3]University of Texas Medical Branch, Galveston, TX, USA

Corresponding Author:
Md. Harun-Or-Rashid, Young Leaders' Program in Healthcare Administration, Nagoya University Graduate School of Medicine, 65 Tsurumai-Cho, Nagoya 466-8550, Japan
Email: mh_rashid67@yahoo.com

Downloaded from aph.sagepub.com at NAGOYA UNIVERSITY MEDICAL LIBRARY on July 24, 2012

increase uptake of HIV testing, the WHO and Joint United Nations program on HIV/AIDS (UNAIDS) also recommended provider-initiated HIV testing and counseling for all TB patients in all settings.[9] In this regard, a study conducted in South India has demonstrated that provider-initiated HIV testing and counseling is acceptable, feasible, and effective under optimum conditions.[10]

The threat of TB along with the toll it takes on HIV/AIDS in some countries has been labeled as alarming by the WHO because the mortality rate for HIV/TB coinfected individuals is high.[11] Cambodia is one of the countries most severely affected by TB and HIV, with a huge potential to have a high coinfection rate. For example, Cambodia was ranked 22nd in the world among countries with a high burden of TB[12] and has a high incidence rate of all forms of TB (495/100 000) and smear-positive pulmonary TB (219/100 000).[11] On the other hand, Cambodia continues to have one of the most serious documented HIV epidemics in Asia, with a prevalence of 1.9% among 15- to 49-year-old adults and an estimated 123 100 adults living with HIV/AIDS.[13] Thus, given that an estimated 64% of Cambodians are infected with *Mycobacterium tuberculosis*,[12] a high HIV/TB coinfection rate is inevitable in this country.

A national HIV seroprevalence surveillance conducted in 2007 among TB patients in Cambodia observed a 7.8% HIV infection rate.[14] As a part of preventive measures to deal with HIV/TB coinfection, the Cambodian Ministry of Health initiated several interventions. In 2006, Cambodia started the National Health Strategic Plan for Tuberculosis Control (2006-2010) with a special emphasis on TB/HIV coinfection prevention. The 2 main objectives of the plan were as follows: (1) to achieve a target where ≥80% of all TB patients referred for HIV are tested by 2010 and (2) to start more than 90% of eligible TB/HIV coinfected patients on antiretroviral therapy.[15] In addition, 233 voluntary counseling and testing (VCT) centers were also established in Cambodia with a special emphasis on identifying HIV infection among TB patients.[16] Although the national referral rate among TB patients for HIV testing was 38% in 2007, 54% in 2008, and 70% in 2009,[17] the referral rate for TB patients in Prey Kabas operational district (OD), Takeo province, was 30% in 2009—the lowest in the Province. This rate was far below the national achievement in the same year and the national target set by the National TB Program. These figures indicate that there are some barriers to the referral procedures for HIV testing in Prey Kabas OD. Thus, identifying the barriers is a prerequisite to making any interventions effective. Barriers to not seeking VCT service have been identified in both developed and developing countries, which include burden for accessing VCT, fear of getting a positive test result, communication barriers, low awareness, and stigma.[18,19] However, most of the barriers were focused on the client's perspective, whereas there is dearth of knowledge about the barriers related to the provider's perspective.

The purpose of this study was to examine the trend of TB patients' referral for HIV during 2007-2009 and to investigate related barriers perceived by health care providers in Prey Kabas OD, Takeo province, Cambodia.

Methods

Study Setting

Prey Kabas OD is located in Takeo province in the southern region of Cambodia. The OD is divided into 3 administrative districts with 260 607 people, 1 referral hospital (RH), 14 health centers (HCs), 2 VCT centers, and 126 health providers. The RH and HCs provide directly observed treatment short course (DOTS) and refer TB patients for HIV testing to VCT centers. TB program officials provide counseling to the patients, draw blood from TB patients, and send the blood specimen to a VCT center. After that, counselors of the VCT centers communicate with respective providers directly about HIV test results.

Downloaded from aph.sagepub.com at NAGOYA UNIVERSITY MEDICAL LIBRARY on July 24, 2012

Study Design and Sample

This study was conducted during August and September 2010. Two sets of data were collected. The first set was obtained from the registers at different HCs and the RH. TB patients registered during January 1, 2007, through December 31, 2009, in all health facilities were included. A checklist with basic demographic information, TB types, and TB patients referred for HIV testing was used to collect the required data. TB patients already diagnosed as HIV positive were excluded. A total of 2375 TB patients were registered at different health facilities from 2007 to 2009 (684 in 2007, 751 in 2008, and 940 in 2009). The second set of data was aimed at identifying the key barriers to TB patients' referral for HIV testing and were collected purposively from all health providers (n = 43) who were involved in referring TB patients for HIV testing. We interviewed 2 types of health providers: (1) managers (n = 9), that is, directors, planners, TB program managers, HIV/AIDS program managers, laboratory supervisors, and pharmacists; and (2) staff of local health services (n = 34), that is, medical doctors, nurses, midwives, counselors, and laboratory technicians. Health providers with <2 years of experience in the TB program were excluded from the study.

Measures

We used a pretested and semistructured questionnaire to conduct face-to-face interviews among health providers. The questionnaire was first prepared in English then translated into Khmer, the Cambodian language, and later back-translated to English to check for inconsistencies. We developed the questionnaire through consultation with health professionals, that is, health sector support project consultants and the National TB Program coordinators. The questionnaire solicited information about demographic variables, health providers' perceptions on barriers to TB patient referral for HIV testing, and ways to improve the referral system. Participation in this study was voluntary. Written informed consent was obtained from the respondents. Respondents were assured of confidentiality of personal information obtained in the study and allowed to decline to participate in this study. Prior permission was also obtained from TB patients registered with different HCs to use their data.

Statistical Analyses

Bivariate comparisons were performed using the χ^2 test, Fisher's exact test, or Student's t test, as appropriate. Multivariable logistic regression was used to identify correlates of TB patient referral for HIV testing after adjusting for center-level variations. Variables were screened for inclusion in an initial multivariable model. Candidate variables with $P \leq .05$ were included in the initial multivariable model. We used logistic regression analysis to examine the trend of TB patient referral for HIV testing parameters during 2007-2009 after adjusting for center-level variations. Year of referral was used as an independent variable (continuous scale), whereas the referral (yes vs no) was used as the dependent variable. All analyses were 2 tailed, and P values <.05 were considered statistically significant. Analyses were performed using SPSS, version 18.0 (SPSS, Chicago, IL) and Stata 11 (Stata Corp, College Station, TX).

Ethical Review

The study was approved by the National Ethics Committee for Health Research, Ministry of Health in Cambodia.

Downloaded from aph.sagepub.com at NAGOYA UNIVERSITY MEDICAL LIBRARY on July 24, 2012

Table 1. TB Patients' Referral Status by Demographics and Year[a]

	2007 (n = 684)		2008 (n = 751)		2009 (n = 940)		Total (n = 2375)	
Characteristics	Registered, n	Referred, n (%)	Registered, n	Referred, n (%)	Registered, n	Referred, n (%)	Registered, n	Referred, n (%)
Gender								
Male	302	16 (5.3)	296	42 (14.2)	456	129 (28.3)	1054	187 (17.7)
Female	382	14 (3.7)	455	74 (16.3)	484	154 (31.8)	1321	242 (18.3)
Age group in years								
<35	95	9 (9.5)	108	21 (19.4)	280	81 (28.9)	483	111 (23.0)
35-60	348	21 (6.0)	374	69 (18.4)	371	113 (30.5)	1093	203 (18.6)
>60	241	0 (0.0)	269	36 (9.7)	289	89 (30.8)	799	115 (14.4)
TB type								
TB smear negative	298	16 (5.4)	234	27 (11.5)	228	147 (25.0)	760	101 (13.3)
TB smear positive	306	12 (3.9)	408	70 (17.2)	489	58 (30.1)	1203	229 (19.0)
Extrapulmonary	80	2 (2.5)	109	19 (17.4)	223	78 (35.0)	412	99 (24.0)
Total	684	30 (4.4)	751	116 (15.4)	940	283 (30.1)	2375	429 (18.0)

Abbreviation: TB, tuberculosis.
[a]Referral rate showed significant upward trend by gender, age groups, and TB type ($P < .001$ for all cases).

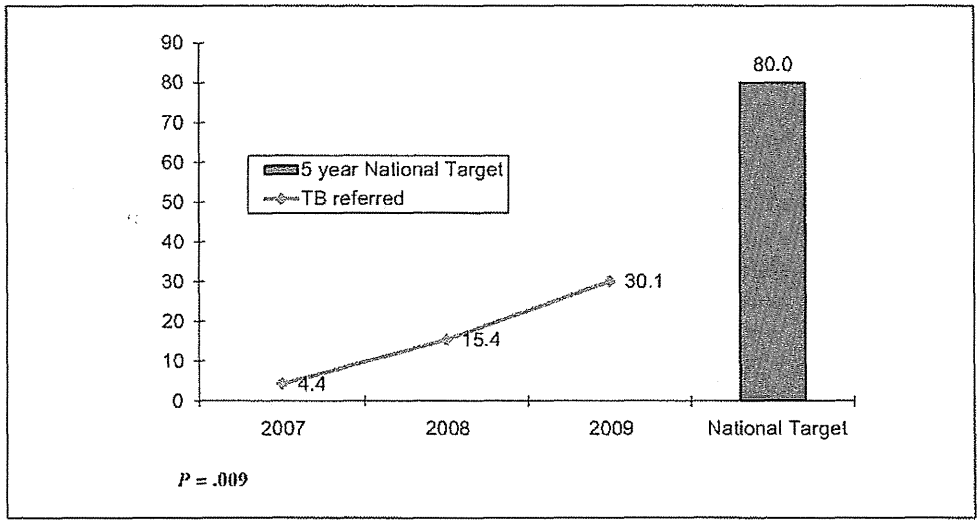


Figure 1. Trend of TB referral for HIV testing during 2007-2009 in comparison with the national target
Abbreviations: TB, tuberculosis; HIV, human immunodeficiency virus.

Results

TB Patients' Demographics and Trend of Referral

Of the 2375 TB patients registered with HCs and the RH during 2007-2009, 55.6% were female, the majority (46.0%) belonged to the 35- to 60-year-old age group, and 50.7% had smear-positive pulmonary TB (Table 1). After adjusting for variation at the HC level, we observed a significant upward trend with regard to TB patient referral as a whole: 4.4% in 2007 to 15.4% in 2008 and finally to 30.1% in 2009 ($P = .009$; Figure 1). The same scenario was observed in

Downloaded from aph.sagepub.com at NAGOYA UNIVERSITY MEDICAL LIBRARY on July 24, 2012

Table 2. Correlates of TB Patients' Referral for HIV Testing

Variables	Referred for HIV Testing		OR[a] (95% CI)	PValue
	Yes	No		
Gender				
Male	187	867	Reference	.387
Female	242	1079	0.91 (0.73-1.13)	
Age group in years				
<35	111	372	1.58 (1.10-2.27)	.012
35-60	203	890	1.33 (0.86-2.06)	.201
>60	115	684	Reference	
TB type				
Smear-negative pulmonary	101	659	Reference	
Smear-positive pulmonary	229	974	1.51 (0.97-2.36)	.067
Extrapulmonary	99	313	1.88 (1.19-2.97)	.007

Abbreviations: TB, tuberculosis; HIV, human immunodeficiency virus; OR, odds ratio; CI, confidence interval.
[a]Odds ratios were adjusted by clustering effect of all health centers.

terms of age, gender, and type of TB ($P < .05$ in all cases except the <35-year-old group and smear-negative pulmonary TB patients). However, the referral rate was far below the national target of 80%.

Correlates of TB Patients' Referral for HIV Testing

The multivariate logistic regression model, after adjusting for center-level variations, showed that age and type of TB were associated with TB patient referral for HIV testing (Table 2). TB patients aged <35 years (OR = 1.58; 95% CI = 1.10-2.27; $P = .012$) were more likely to be referred for HIV testing compared with the >60-year-old group. A similar scenario was observed for smear-positive (OR = 1.51; 95% CI = 0.97-2.36; $P = .067$) and extrapulmonary TB (OR = 1.88; 95% CI = 1.19-2.97; $P = .007$), although the former category did not achieve statistical significance at the $P < .05$ level. Referral rate did not vary by gender in the multivariate model.

Health Providers' Perceptions Regarding Barriers to Referring TB Patients for HIV Testing

Table 3 compares the frequency of perception of different barriers among health providers—that is, managers and local health staff. By and large, managers and health staff differed with regard to perception of barriers. Almost all health staff agreed on the barriers like "poor knowledge about TB/HIV," "lack of communication skill," "insufficient financial support," and "absence of target plan." On the other hand, only about half of the managers agreed on the same barriers. Three fourths of the health staff also agreed on the existence of "fear of knowing test result/stigma" and "strategy and guideline are not available in place," which was much higher than the proportion of managers. On the other hand, the majority of the managers felt that "poor commitment from local health staff" was an important barrier, whereas only 21% of the health staff agreed on it.

Downloaded from aph.sagepub.com at NAGOYA UNIVERSITY MEDICAL LIBRARY on July 24, 2012

Table 3. Health Providers' Perceptions Regarding Barriers to Referring TB Patients for HIV Testing

Health Providers' Perceptions	Managers (n = 9) n (%)	Local Health Staff (n = 34) n (%)	*P* Value
Poor knowledge about TB/HIV	6 (66.7)	33 (97.1)	.024
Lack of communication skills (counseling for HIV testing)	6 (66.7)	33 (97.1)	.024
Insufficient financial support for transportation/ incentive	5 (55.6)	33 (97.1)	.005
Absence of target plan of TB patients referred in AOP	4 (44.4)	32 (94.1)	.002
Fear of knowing test result/stigma among TB patients	2 (22.2)	28 (82.4)	.001
Strategies and guidelines are not in place	3 (33.3)	26 (76.5)	.040
Limited VCT center	3 (33.3)	11 (32.4)	1.000
Poor commitment from health staff	7 (77.8)	7 (20.6)	.003
Poor collaboration between TB and HIV/AIDS program	4 (44.4)	2 (5.9)	.012

Abbreviations: TB, tuberculosis; HIV, human immunodeficiency virus; AOP, annual operational plan; VCT, voluntary counseling and testing; AIDS, acquired immune deficiency syndrome.

Discussion

We observed that a large proportion of TB patients were not referred for HIV testing in this area of Cambodia. Our finding that the majority of providers perceived the existence of certain barriers to the referral process indicates that appropriate interventions could improve the referral process. Furthermore, the differences in perception of barriers between managers and health staff observed in this study could be the topic of future qualitative studies to generate appropriate intervention programs.

Early identification of HIV among TB patients along with counseling is one of the key strategies to achieve the TB-related millennium development goals.[19] Several studies conducted in Africa (53% to 95%)[20,21] and India (72%),[22] where the burden of coinfection is very high, also showed moderately high referral rates. However, compared with those countries, we observed a lower referral rate, which is even far below the respective provincial (61%) and national (70%) rates during the same time frame.[17] This situation clearly indicates that Pres Kabas OD is far away from achieving the national target of an 80% referral rate.[15] Several factors observed in this study might explain this low achievement and the associated barriers, that is, lack of smooth access to VCT, poor knowledge of TB/HIV among TB patients and providers, poor patient-provider communication with regard to referral for HIV testing, absence of strategic approach for the referral, insufficient financial support for transportation, and fear of knowing the test results and associated stigma. These factors are consistent with the findings reported in studies related to TB/HIV from Cambodia,[23,24] Vietnam,[25] Indonesia, and Africa.[18,19,26] Studies conducted in developed countries[27,28] also identified poor knowledge of TB/HIV as one of the main barriers to referral of TB patients for HIV testing.[27,28]

The referral system for TB patients has not been in existence for a long time in Cambodia. Thus, lack of practical experience and lack of appropriate awareness on the importance of timely referral of TB cases for HIV testing and the fatal consequences of TB/HIV coinfections might also have played important roles in the low referral rate. However, the upward trend of TB patient referral for HIV testing during 2007-2009 implies that there is gradual improvement in

Downloaded from aph.sagepub.com at NAGOYA UNIVERSITY MEDICAL LIBRARY on July 24, 2012

the situation. Support with regard to different components of the referral system, for example, transportation of blood specimen from the health center to the VCT by nongovernmental organizations and Global Fund, were also responsible for the improvement.

We are unable to shed light on the reasons for the low referral rate in Prey Kabas OD area compared with the rest of the country. Some regional differences such as the rural nature of this province and differences in other social indicators might have played a role in this regard. There is a notion among policy makers and providers that nongovernmental organizations' activities with regard to TB/HIV control in this area are less evident than in other parts of the country. Cultural differences also cannot be ruled out. However, these are speculations only because we did not gather any data with regard to these issues. On the other hand, there is a dearth of information in the literature to support our speculations. Future explorative studies are needed to examine the difference in referral rates in different areas in the country based on nationally representative data.

Our study identified some sort of differences between the managers and local health staff with regard to different barriers. For example, "poor commitment from the health staff" was identified as a key barrier to referral by the managers, whereas local health staff identified poor knowledge, lack of communication skills, insufficient financial support, and absence of a target plan as the main barriers. This discordance with regard to barriers reflects the existence of gaps in coordination and warrants tailored interventions for the managers and health staff. Interventions such as strengthening coordination among TB control staff, a comprehensive budget plan, training in communication skill development, and financial incentives, as suggested by WHO, could play an important role in increasing the referral rate.[29]

There were several limitations to our study. First, our findings may not be generalizable because the study was based on just 1 OD in Cambodia. Second, the number of respondents to explore the barriers to TB patient referral for HIV testing was very small. Third, barriers generated in this study were based on providers' opinions about the low referral rate rather than their actual experience. Finally, only a quantitative study design was used to explore the barriers to TB patient referral for HIV testing. However, the results generated by this small study could be used as pilot data for future larger studies based on a mixed-method design.

Conclusion

In conclusion, this study highlighted the fact that the referral rate of TB patients for HIV testing in Prey Kabas OD area was low. Findings of this study may be useful to plan for appropriate intervention programs to achieve the national target of an 80% referral rate among TB patients for HIV testing.

Acknowledgments

The authors acknowledge the contributions of Dr Vijay Rao, Health Sector Support Project consultant; Dr Khun Kim Eam, National TB coordinator, National TB program; and Dr Hing Samith, Prey Kabas OD director, Takeo province, Ministry of Health, Cambodia, to this study.

Declaration of Conflicting Interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The author(s) disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported in part by the nonprofit organization Epidemiological & Clinical Research Information Network (ECRIN).

Downloaded from aph.sagepub.com at NAGOYA UNIVERSITY MEDICAL LIBRARY on July 24, 2012

References

1. Cain KP, McCarthy KD, Heilig CM, et al. An algorithm for tuberculosis screening and diagnosis in people with HIV. *N Engl J Med*. 2010;362:707-716.
2. Nguyen LT, Christoffersen SV, Rasch V. Uptake of prenatal HIV testing in Hai Phong Province, Vietnam. *Asia Pac J Public Health*. 2010;22:451-459.
3. Akksilp S, Karnkawinpong O, Wattanaamornkiat W, et al. Antiretroviral therapy during tuberculosis treatment and marked reduction in death rate of HIV-infected patients, Thailand. *Emerg Infect Dis*. 2007;13:1001-1007.
4. Cain KP, Kanara N, Laserson KF, et al. The epidemiology of HIV-associated tuberculosis in rural Cambodia. *Int J Tuberc Lung Dis*. 2007;11:1008-1013.
5. Manosuthi W, Chottanapand S, Thongyen S, Chaovavanich A, Sungkanuparph S. Survival rate and risk factors of mortality among HIV/tuberculosis-coinfected patients with and without antiretroviral therapy. *J Acquir Immune Defic Syndr*. 2006;43:42-46.
6. Mukadi YD, Maher D, Harries A. Tuberculosis case fatality rates in high HIV prevalence populations in sub-Saharan Africa. *AIDS*. 2001;15:143-152.
7. Quy HT, Cobelens FG, Lan NT, Buu TN, Lambregts CS, Borgdorff MW. Treatment outcomes by drug resistance and HIV status among tuberculosis patients in Ho Chi Minh City, Vietnam. *Int J Tuberc Lung Dis*. 2006;10:45-51.
8. Getahun H, Gorkom Jv, Harries A, et al. *Interim Policy on Collaborative TB/HIV Activities*. Geneva, Switzerland: Stop TB Department and Department of HIV/AIDS; 2004.
9. World Health Organization (WHO), UNAIDS. *Guidance on Provider-Initiated HIV Testing and Counselling in Health Facilities*. Geneva, Switzerland: WHO; 2007. http://www.who.int/hiv/pub/guidelines/9789241595568_en.pdf. Accessed June 30, 2011.
10. Thomas BE, Dewan PK, Vijay S, et al. Perceptions of tuberculosis patients on provider-initiated HIV testing and counseling: a study from South India. *PLoS One*. 2009;4:e8389.
11. World Health Organization (WHO). *Global Tuberculosis Control: Epidemiology, Strategy, Financing*. Geneva, Switzerland: WHO; 2009.
12. Eang MT, Chheng P, Natpratan C, Kimerling ME. Lessons from TB/HIV integration in Cambodia. *Bull World Health Organ*. 2007;85:382-383.
13. Ministry of Health. *HIV Sentinels Surveillance (HSS) in Cambodia*. Phnom Penh, Cambodia: Center for HIV/AIDS, Dermatology and STD; 2003.
14. National Center for Tuberculosis and Leprosy Control. *National HIV Sero-Prevalence Surveillance Amongst TB Patients in Cambodia, 2007*. Phnom Penh, Cambodia: National Center for Tuberculosis and Leprosy Control; 2007.
15. Ministry of Health. *National Health Strategic Plan for TB Control, 2006-2010*. Phnom Penh, Cambodia: Center for HIV/AIDS, Dermatology and STD; 2006.
16. Yi S, Poudel KC, Yasuoka J, Ichikawa M, Tan V, Jimba M. Influencing factors for seeking HIV voluntary counseling and testing among tuberculosis patients in Cambodia. *AIDS Care*. 2009;21:529-534.
17. National Tuberculosis Program. *Ministry of Health Report: 2009*. Phnom Penh, Cambodia: Ministry of Health; 2009.
18. Mahendradhata Y, Ahmad RA, Lefevre P, Boelaert M, Van der Stuyft P. Barriers for introducing HIV testing among tuberculosis patients in Jogjakarta, Indonesia: a qualitative study. *BMC Public Health*. 2008;8:385.
19. Ayenew A, Leykun A, Colebunders R, Deribew A. Predictors of HIV testing among patients with tuberculosis in North West Ethiopia: a case-control study. *PLoS One*. 2010;5:e9702.
20. Topp SM, Chipukuma JM, Giganti M, et al. Strengthening health systems at facility-level: feasibility of integrating antiretroviral therapy into primary health care services in Lusaka, Zambia. *PLoS One*. 2010;5:e11522.

Downloaded from aph.sagepub.com at NAGOYA UNIVERSITY MEDICAL LIBRARY on July 24, 2012