

Present Status and Perspectives of Colorectal Cancer in Asia: Colorectal Cancer Working Group Report in 30th Asia-Pacific Cancer Conference

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Objective: To reveal the present status and future directions of colorectal cancer in Asia.

Methods: The Working Group consisted of oncologists from six Asian countries (Japan, Korea, Hong Kong, China, Taiwan, Singapore and Philippines) discussed colorectal cancer in the 30th Asia-Pacific Cancer Conference and made a consensus report.

Results: The incidence of colorectal cancer has been increasing rapidly in recent decades, and mortality has also increased except in Japan and Singapore. Colorectal screening with fecal occult blood tests is a national policy in Taiwan, Japan and Korea. Total colonoscopy is the most common examination for diagnosing colorectal cancers and neoplasms. However, there are differences in the macroscopic classification used. Laparoscopic surgery for colon cancer is extensively used, although the indication varies. Adequate lymph node harvesting of more than 12 nodes is performed in most countries. Neoadjuvant chemoradiation therapy is not routinely done for T2 or T3 rectal cancer. Total mesorectal excision is the standard surgery for rectal cancer. Survival rate data are unavailable for many countries and should be compiled in all. The differences in the health-care delivery systems affect the treatment choices for unresectable colorectal cancer. Infusional 5-FU plus leucovorin plus oxaliplatin (FOLFOX) is the most popular first-line regimen. Cetuximab is mainly used as a second- or third-line regimen with reference to *k-ras* mutation. Oxaliplatin-based adjuvant chemotherapy is commonly used for stage III disease, whereas the clinical practice for stage II disease varies.

Conclusions: Further clinical cooperation is needed to optimize the management of colorectal cancer in Asia.

Key words: colorectal cancer – screening – diagnosis – surgery – chemotherapy

INTRODUCTION

The Working Group, consisting of 12 expert oncologists for colorectal cancer from six Asian countries (Japan, Korea, Hong Kong, China, Taiwan, Singapore and Philippines), discussed screening, diagnosis, surgery and chemotherapy, based on their reply to a questionnaire (appendix). Dr Suzuki (the secretary of this working group) had made the questionnaire

and sent it to all members (authors of this manuscript) of the working group in advance. Then, he obtained their replies and summarized the results as a the material of the meeting in the 30th Asia-Pacific Cancer Conference (APCC). The discussion points were the following: (i) incidence, mortality rate and cancer screening, (ii) endoscopy, (iii) surgery and (iv) chemotherapy for colorectal cancer.

INCIDENCE, MORTALITY RATE AND CANCER SCREENING

The incidence of colorectal cancer has been increasing rapidly in the Asian area in the last few decades. The mortality of colorectal cancer has been increasing in the last decade in Asian countries, except in Japan and Singapore (Fig. 1). Colorectal cancer screening systems have been launched as a national policy in Taiwan, Japan and Korea, but national screening programs do not exist in some Asian countries. Screening is conducted for males and females who are 40 years old or more in Japan and at least 50 years old in Korea. In Taiwan, the target age for screening is from 50 to 69 years of age. Immunological or chemical fecal occult blood tests are used as the screening methods. For more detailed examination, total colonoscopy is conducted as the method of first choice. In Taiwan and Japan, the colorectal screening rate for the local population is ~25%. Colorectal cancer screening can decrease mortality (1), however, the screening rate in Asia is quite low compared with Western countries (2).

Fecal occult blood tests for screening and total colonoscopy for close examination should be recommended in countries with a high prevalence of colorectal cancer. Budget support from all sectors is needed for colorectal cancer screening. Education and advocacy to the public need to be strengthened.

COLORECTAL ENDOSCOPY

Colonoscopy is now the most widely accepted and popular examination for diagnosis of colorectal cancer, and total colonoscopy is also the common pathway and goal of all screening tests. The macroscopic morphology is directly linked to the biological behavior and the risk of malignant transformation or deep invasion of colorectal neoplasms (3). Both the Paris classification and the Japanese classification are popular for classification of superficial GI tract

neoplasms. Depressed-type colorectal neoplasms carry a higher risk of malignant transformation and they invade deep into the submucosal layer even when still relatively small in size, compared with flat or polypoid colorectal neoplasms. A survey of the application of macroscopic classification in Asian countries showed that Hong Kong, Taiwan, Japan and Korea widely use macroscopic or endoscopic classification, whereas Singapore and the Philippines do not use macroscopic classification in colonoscopic examinations. The Japanese classification is more popular in Japan, whereas the Paris classification that was published in 2002 is more popular in Korea. Both classification systems are widely used in Taiwan.

Colorectal endoscopy is important for delineating the margin and determining the surface characteristics of colorectal neoplasms. After magnification or dye spraying, endoscopy can define the area of malignant transformation and, moreover, can predict the depth of invasion, which determines the optimal treatment strategy. The survey found that the modality used to diagnose or predict the depth of invasion of colorectal cancer differs among countries. Most countries use biopsy as the gold standard, but in Taiwan and Japan the dye-spraying method and magnified observation are more popular for characterizing the nature of colorectal neoplasms.

Polypectomy is the most widely used procedure for resecting colorectal neoplasms. Endoscopic mucosal resection is popular in most countries, whereas endoscopic submucosal dissection is less common but used more in Japan and Korea. Analysis of surgical pathological specimens in Japan showed that the risk of local lymph node metastasis is near zero if the depth of invasion is <1000 μm (4). In both Japan and Korea, if the depth of invasion is <1000 μm and the lesion is a histologically well-differentiated adenocarcinoma, it is acceptable to perform endoscopic resection, and further surgical resection is not necessary. In Singapore, mainly the depth of invasion and the Haggitt classification are used to determine whether surgical resection is necessary or not.

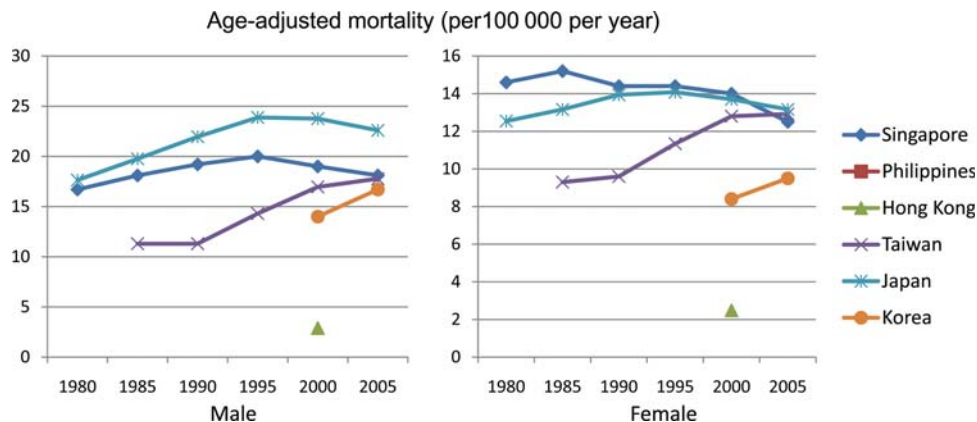


Figure 1. Age-adjusted mortality of colorectal cancer in Asia.

In conclusion, total colonoscopy is currently the most widely used examination to diagnose colorectal cancers and neoplasms in the Asia-Pacific region. However, there are some differences and a lack of consensus regarding macroscopic classification of colorectal neoplasms among countries. The modality that is used to characterize and diagnose colorectal neoplasms also differs among countries. To unify and standardize the endoscopic diagnosis and treatment procedure for colorectal cancer, a common guideline would be required in the Asia-Pacific region. Also, the quality of colonoscopy should be emphasized.

SURGERY

Laparoscopic surgery is actively performed in three countries, Singapore, Japan and Korea; yet, many colorectal surgeons in Hong Kong are also experienced in it. As for the indication, Singapore, the Philippines and Korea usually perform colon resection for most patients using laparoscopic techniques. The exception is extremely difficult cases, such as T4, intestinal obstruction, a history of previous laparotomy, etc. However, especially in Japan, laparoscopic surgery is currently recommended only for T1 or T2 tumor of colon and rectum, and not for low rectal cancer. The penetration rate was only 10% in the Philippines, in contrast to around a 50% rate in Korea and 60% in Japan. In four countries, Singapore, Hong Kong, Japan and Korea, they usually harvest more than 12 lymph nodes in the usual colectomy, but in the Philippines they usually harvest <12 nodes. For clinical T2 or T3 rectal cancer, most surgeons in Asia do not usually recommend preoperative chemoradiation. Regarding the extent of lymph node dissection in rectal cancer, the surgeons in Singapore, Hong Kong and Japan usually perform lateral lymph node dissection for T3 rectal cancer, but the surgeons in the Philippines and Korea do not. Total mesorectal excision (TME) for rectal cancer is the affirmatively standard operation. With regard to the 5-year survival rates for colorectal cancer, they are similar for stage I and stage II, for example, around a 90% 5-year survival rate for stage I and an 80% 5-year survival rate for stage II in Japan and Korea (Table 1). However, there was some difference in the

two countries' results for stage III colorectal cancer. In Japan, the 5-year survival rate is over 70%, compared with a lower rate of around 50% in Korea.

In conclusion, laparoscopic surgery for colon cancer is widely performed, although the indication varies among the countries. Second, adequate lymph node harvesting is generally performed in most countries. Third, neoadjuvant chemoradiation therapy is not routinely done for T2 or T3 rectal cancer. Fourth, TME is the standard surgery for rectal cancer. Fifth, survival rate data are not available for many countries other than Japan and Korea.

The consensus and recommendations regarding the future strategy for colorectal cancer surgery in Asian countries are that nationwide exact data should be compiled in all countries, clinical trials are needed to evaluate the respective roles of preoperative chemoradiation and lateral pelvic node dissection, and the surgical techniques for colorectal cancer need to be standardized.

CHEMOTHERAPY

Much evidence has been generated in Western countries by large clinical trials, and there are some guidelines for chemotherapy of colorectal cancer (5). For unresectable metastatic colorectal cancer, 5-FU plus leucovorin plus oxaliplatin (FOLFOX) plus bevacizumab or infusional 5-FU plus leucovorin plus irinotecan (FOLFIRI) plus bevacizumab is recommended in the western guidelines, but in Asia the prevalence of use is 30–40% only in Japan (Table 2). In other countries, the most popular regimen is FOLFOX without bevacizumab. In Singapore, the prevalence of use is very similar for each regimen. Selection of the treatment regimen is affected by the medical fees. In Japan, all valid therapies are covered by social medical insurance, whereas in other countries the patients have to pay for themselves. In most countries, cetuximab is placed as a second-line or third-line treatment, with or without irinotecan. Patients with mutant-type K-Ras gene get no benefit from cetuximab (5). Therefore, K-Ras mutations are checked before using cetuximab in almost all countries, but not in Japan, where the K-Ras mutation test has not yet

Table 1. Five-year survival rates of colorectal cancer

	Stage I (%)			Stage II (%)			Stage III (%)			Stage IV (%)		
	C	R	T	C	R	T	C	R	T	C	R	T
Taiwan	85.3	73.1	—	75.5	65.1	—	47.8	56.4	—	10.3	12.5	—
Japan	90.6	89.3	90.6	83.6	76.4	81.2	71.3	58.2	66.3	14.3	11.1	13.2
Korea	—	—	90	—	—	70	—	—	50	—	—	>5

Stage I, T_{1,2}N₀M₀; Stage II, T_{3,4}N₀M₀; Stage III, T_{any}N_{1,2}M₀; Stage IV, T_{any}N_{any}M₁; C, Colon; R, Rectum; T, Total.

Table 2. Proportions (%) of the first-line regimen for unresectable metastatic colorectal

	Singapore	Philippines	Hong Kong	Taiwan	Japan	Korea
5-FU/LV	10	25	10	10	3–5	
5-FU/LV + bevacizumab	0	5	0		0–2	
FOLFOX	25	50	40	50	40–60	60
FOLFOX + bevacizumab	10	6	5	5	25–35	5
FOLFIRI	25	5	40	20	5	15
FOLFIRI + bevacizumab	10	4	5	5	5	3
XELOX	10					15
SOL					1–5	
XELOX + bevacizumab	10					
UFT + LV		5			1	
FOLFOX or FOLFIRI + cetuximab				10		2

5-FU, 5-fluorouracil; LV, leucovorin; XELOX, capecitabin plus oxaliplatin; SOL, S-1 plus oxaliplatin.

Table 3. The most popular adjuvant chemotherapy for colon cancer in each country

	Singapore	Philippines	Hong Kong	Taiwan	Japan	Korea
Stage II	5-FU/LV, capecitabine	FOLFOX	5-FU/LV	5-FU/LV	UFT	5-FU/LV (low risk), FOLFOX, capecitabine (high risk)
Stage III	FOLFOX, XELOX	FOLFOX	5-FU/LV, FOLFOX	FOLFOX	5-FU/LV, UFT/LV, capecitabine	FOLFOX, capecitabine

been approved. With regard to the adjuvant chemotherapy for colon cancer, stage II and III disease were handled separately (Table 3). In most countries, a 5-FU-based regimen, not containing oxaliplatin, is routinely used for the adjuvant setting for stage II colon cancer. For stage III colon cancer, most countries except for Japan use a FOLFOX or XELOX regimen. The reason for this discrepancy is that FOLFOX for the adjuvant setting has been just approved in Japan in October 2009. The duration of adjuvant therapy was 6 months in all countries.

In conclusion, differences in the health-care delivery systems significantly affect the treatment choices for unresectable colorectal cancer. FOLFOX is the most popular first-line regimen for unresectable and metastatic colorectal cancer. Cetuximab is mainly used as the second- or third-line regimen, with or without irinotecan. K-Ras mutation testing is usually performed before cetuximab use. Oxaliplatin-based adjuvant chemotherapy is commonly used for stage III colon disease, whereas the clinical practice for stage II disease varies among the countries.

In conclusion, clinical cooperation is strongly needed to optimize the management of colorectal cancer in Asia.

Funding

This study was supported by the funding from the secretariat of the 30th Asia-Pacific Cancer Conference and Chugai Pharmaceutical Company.

Conflict of interest statement

None declared.

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Appendix

Epidemiology

Q1, How is age-adjusted morbidity and mortality rate of CRC in your country? (if available)

Age-Adjusted morbidity	Total No.(per 100,000)	Male No. (per 100,000)	Female No. (per 100,000)
1978-1982			
1983-1987			
1988-1992			
1993-1997			
1998-2002			
2003-2007			

Age-Adjusted mortality	Total No.(per 100,000)	Male No. (per 100,000)	Female No. (per 100,000)
1978-1982			
1983-1987			
1988-1992			
1993-1997			
1998-2002			
2003-2007			

The number should be total amount of 5year period.
When you do not have any applicable data the above format, but have some similar data, could you write them down in the next box or provide the corresponding material copy?

CRC screening

Q2, Are there any CRC screening systems in your country?
• Yes / • No (if yes, go to Q3,4,5,6,7. if no, go to Q8,9)

Q3, What is the subject and method for cancer screening?

Eligibility for subject

Age : • more than _____ years old, • From _____ years old to _____ years old
• Not decided

Sex : • Male, • Female, • Both, • Not decided

Food habits: • considered or • not considered

Family history of cancer : • considered or • not considered

Others

Screening method

• Fecal occult blood test (Chemical)
• Fecal occult blood test (Immunological)

Others

Further close examination recommended when positive for screening

• Total colonoscopy, • Sigmoidoscopy,
• Sigmoidoscopy+X-ray exam with barium enema,
• X-ray exam with barium enema, • Not decided

Q4, What is the most recent screening rate? (if available)
Average %

Q5, What is the most recent positive rate in screening exam? (if available)
Average %

Q6, What is the most recent close exam rate? (if available)
Average %

Q7, What is the finding rate for CRC? (if available)
Early cancer Average %
Advanced cancer Average %

Q8, Do you think CRC screening system should be established?

- Yes (please go to Q9)
- No (Why?)

Q9, What do you think is important to establish it? (Multiple choice)

- Budget
- Public agreement
- Announcement
- Others

Endoscopy

Q10, Which is popular exam to find CRC in your country?
• Total colonoscopy • Sigmoidoscopy • Others

Q11, Do you use macroscopic classification for early cancer lesions in your country?
• Yes (go to Q12)
• No (go to Q13)

Q12, Which classification is used for them?

- The Paris Endoscopic Classification 2002 (Is, Ila, Ilc, etc.)
- WHO(IARC) Classification(exophytic/fungating, endophytic/ulcerative, etc.)
- Bockus Gastroenterology Classification(polypoid mass, annular, etc.)
- Japanese Classification of Colorectal Carcinoma (JSCCR) (Is, Ila, Ilc, etc.)
- Original classification (please attach a copy)
- Others

Q13, How frequently do you use following methods for endoscopic diagnosis of adenoma or early cancer?

	Your institution %					In general % (in your country)				
	0	~25	~50	~75	~100	0	~25	~50	~75	~100
Biopsy										
dye method										
Magnified observation										
EUS										

Q14, How frequently do you use following procedure for endoscopic resection for early colorectal carcinoma?

	Your institution				In general (in your country)			
	1	2	3	4	1	2	3	4
Polypectomy								
EMR (Endoscopic Mucosal Resection)								
ESD (Endoscopic Submucosal Dissection)								

1: not done, 2: uncommon, 3: sometimes done, 4: common

Q15, Do you have any criteria for additional surgical resection after endoscopic resection?

- Yes such as
- No

Surgery
Colon cancer

Q16, Do you have an experience of laparoscopic surgery?

- Yes (go to Q17,18, 19)
- No (go to Q19)

Q17, What are the indications for laparoscopic surgery?

Q18, What is the frequency of laparoscopic surgery?
% per indicated cases

Q19, What is the number of lymph-nodes dissection in usual colectomy?
• Less than 12 • More than 12

Rectal cancer

Q20, For T2 or T3 rectal cancer, do you routinely do chemoradiation therapy before surgery?

- Yes
- No

Q21, Do you do lateral lymph-nodes dissection for T3 rectal cancer?

- Yes
- No

Q22, Do you do TME (Total Mesorectal Excision)?

- Yes
- No

Colorectal cancer

Q23, How is 5-years survival rates of CRC? (if available)

	Your institution %			In general % (in your country)		
	Colon	Rectum	Total	Colon	Rectum	Total
Stage I						
Stage II						
Stage III						
Stage IV						

Stage is based on 6th TNM classification.

Please give the data separating colon and rectum, if you could.

Chemotherapy

Q24, What is the popular first-line regimen for unresectable metastatic CRC?

	Your institution %	In general % (in your country)
5FU/LV		
5FU/LV+Bevacizumab		
FOLFOX		
FOLFOX +Bevacizumab		
FOLFIRI		
FOLFIRI +Bevacizumab		
Other		
Other		
Total	100	100

Q25, What are the indications of cetuximab in your institution?

- First line with FOLFIRI or FOLFOX (How frequently? %)
- Second or third line with or without CPT-11 (How frequently? %)
- Monotheapy with cetuzimab in the third line (How frequently? %)
- Not decided
- Available but never use (Why?)
- Not available (Why?)

Q26, Do you usually check KRAS mu tation before cetuximab use?

- Yes
- No

How about in your country?

Q27, What is the most popular adjuvat chemotherapy for colon cancer in your country?

- Stage II
- Stage III

Q28, How long is the adjuvant chemotherapy?

- Less than 6 months (months),
- 6 months,
- More than 6 months (months)