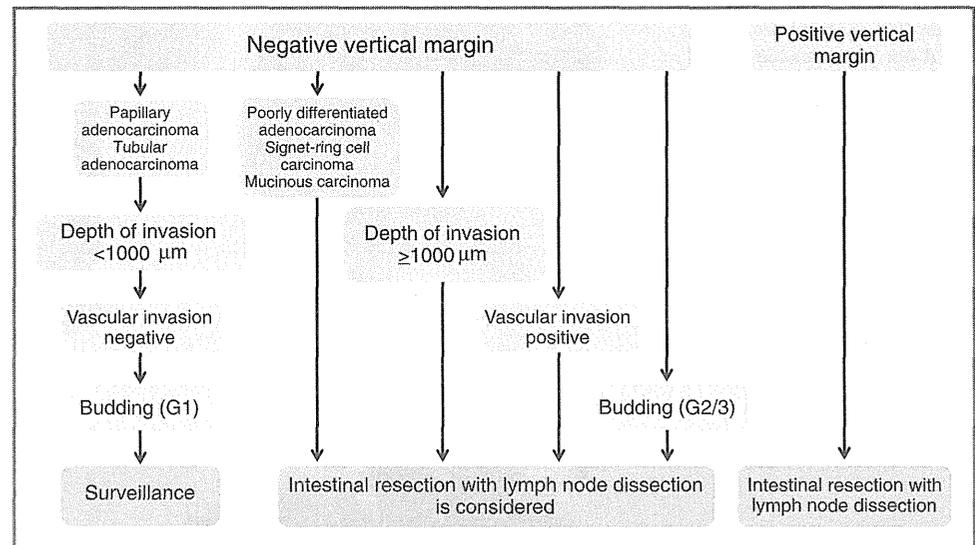


Table 10 Comparison between the recurrence rates of colon cancer and rectal cancer according to the site of the first recurrence (RS cancer was counted as colon cancer)

Site of recurrence	Colon cancer (3,583 patients)	Rectal cancer (1,647 patients)	<i>p</i> value
Liver	7.0% (252)	7.3% (121)	NS
Lung	3.5% (126)	7.5% (124)	<0.0001
Local	1.8% (64)	8.8% (145)	0.0001
Anastomotic	0.3% (9)	0.8% (13)	0.0052
Other	3.6% (130)	4.2% (69)	NS
All	14.1% (506)	24.3% (400)	<0.0001

Project study of the JSCCR: patients in years 1991–1996

Fig. 10 Treatment strategies for pSM cancer after endoscopic resection



[Surveillance of metachronous multiple primary cancer]

- A past medical history of colorectal cancer, regardless of stage, is a risk factor for metachronous colorectal cancer [77].
- The recommended interval between colonoscopy ranged from 1 to 5 years, depending on the report [78].
- There was no evidence indicating the necessity of periodic detailed examinations for cancer in other organs (multiple cancer) after surgery for colorectal cancer (CQ-19).

Clinical questions

CQ-1: Indication criteria for additional treatment after endoscopic resection (Fig. 10)

Recommendation: Category B

- Surgical resection is preferable when the vertical margin is positive.
- If any of the following findings is observed during histological examination of the resected specimen,

intestinal resection with lymph node dissection is considered as an additional treatment:

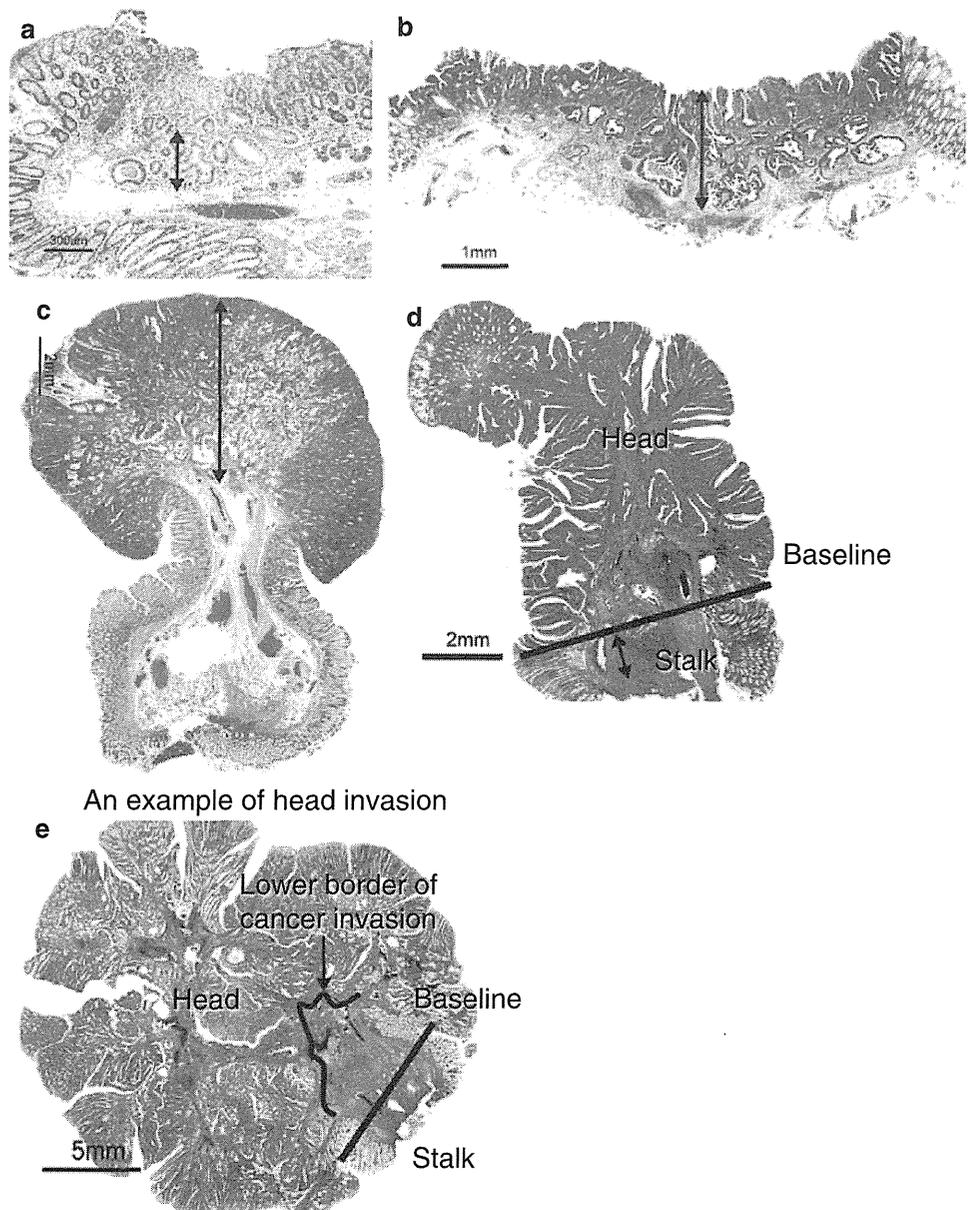
- (1) Depth of SM invasion $\geq 1,000 \mu\text{m}$,
- (2) vascular invasion positive,
- (3) poorly differentiated adenocarcinoma, signet-ring cell carcinoma, or mucinous carcinoma [79],
- (4) Grade 2/3 budding at the site of deepest invasion [79].

Note:

- “Vertical margin-positive” means that carcinoma is exposed at the submucosal margin of the resected specimen.
- Depth of SM invasion is measured by the method described in “Side Memo 1” (Fig. 11).
- Vascular invasion consists of lymphatic and venous invasion (Figs. 12, 13, 14).
- The method for assessing budding is described in Fig. 15.

The principle for the treatment of pSM carcinomas, which are invasive carcinomas, is intestinal resection with lymph node dissection. However, some pSM carcinomas have a very low risk of metastasis, and the purpose of these

Fig. 11 Method for measuring depth of SM invasion. **a** When it is possible to identify or estimate the location of the muscularis mucosae, depth of SM invasion is measured from the lower border of the muscularis mucosae. **b, c** When it is not possible to identify or estimate the location of the muscularis mucosae, depth of SM invasion is measured from the surface layer of the muscularis mucosae. Sessile lesion (**b**), pedunculated lesion (**c**). **d** For pedunculated lesions with tangled muscularis mucosae, depth of SM invasion is measured as the distance between the point of deepest invasion and the reference line, which is defined as the boundary between the tumor head and the stalk. **e** Invasion by pedunculated lesions that is limited to within the head is defined as “head invasion.”



criteria is to minimize the need for additional resections that eventually result in overtreatment of such patients. While no diagnostic methods make it possible to predict lymph node metastasis (pN) without fail, the degree of risk of metastasis can be used as a basis for determining whether or not to perform additional treatment.

Factors such as the depth of submucosal invasion (SM invasion depth) [80], histological type (such as poorly differentiated adenocarcinoma, signet-ring cell carcinoma, and mucinous carcinoma [79]), the presence of a poorly differentiated area and mucinodules at the site of deepest invasion, budding, and vascular invasion have been reported to be risk factors for regional lymph node metastasis by pSM carcinoma [79, 81].

The above criteria for determining whether additional treatment is indicated were prepared based on the following 3 criteria for performing additional intestinal resection of pSM carcinoma described in the *Japanese Classification of Colorectal Carcinoma* (2nd edition, 1980): (1) obvious intravascular carcinoma invasion; (2) poorly differentiated adenocarcinoma or undifferentiated carcinoma; (3) massive carcinoma invasion extending to the vicinity of the margin [82]. The description of “massive carcinoma invasion” in the 4th edition of the *Japanese Classification of Colorectal Carcinoma* was revised to the following more specific description in the 5th edition (1994): invasion deeper than “very shallow invasion” (e.g., invasion exceeding approximately 200 to 300 µm) [83].

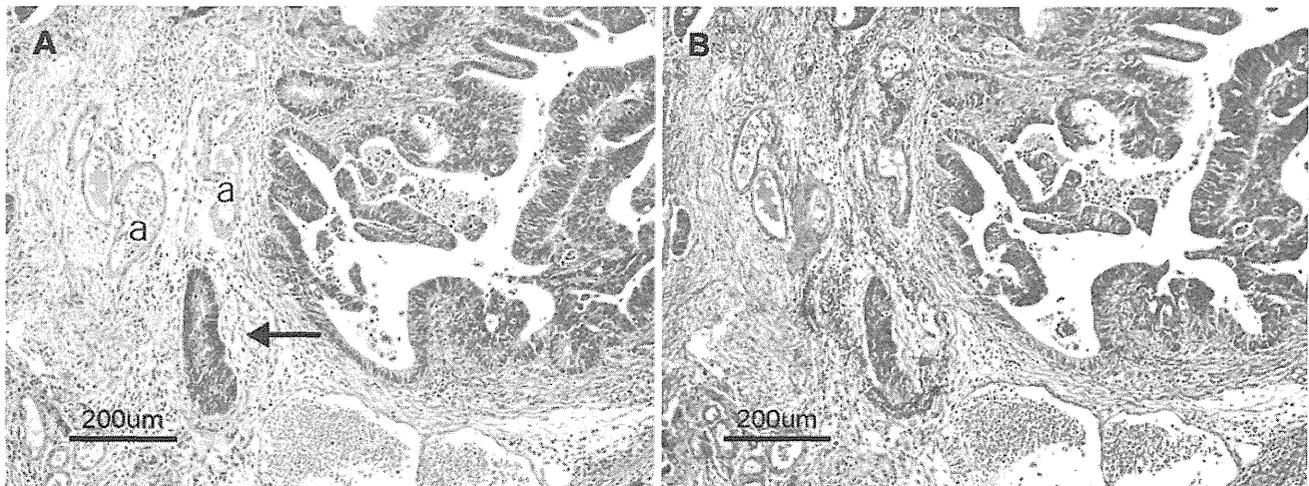


Fig. 12 Venous invasion (*arrow* in **a**). **a** Located in the vicinity of an artery (*a*). **b** Elastic fibers in the vein wall have been highlighted by Victoria blue staining

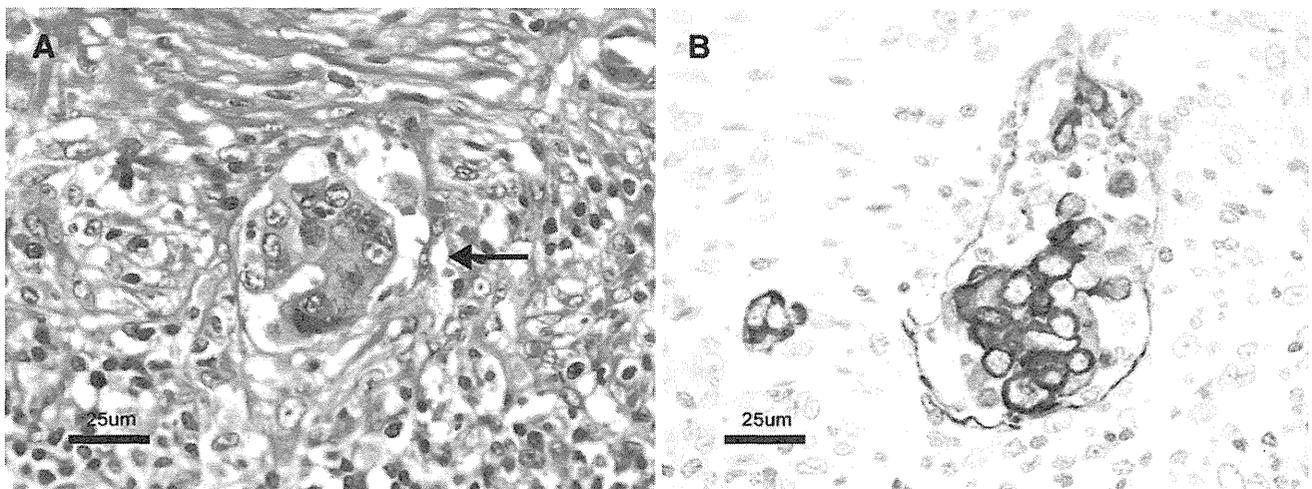


Fig. 13 Lymphatic invasion (*arrow* in **a**). **a** A cancer cell nest is visible in the interstitial space. **b** Double staining for cytokeratin and D2-40. Cancer cells are stained *brown*, and the lymphatic endothelium is stained *purplish red*

Subsequent case series studies in Japan have shown that “200–300 μm ” can be extended to 1,000 μm [84]. According to the results of the project study by the JSCCR, the lymph node metastasis rate of colorectal carcinoma with an SM invasion depth of 1,000 μm or more was 12.5% (Table 11) [80, 84]. However, approximately 90% of patients with a depth of invasion of 1,000 μm or more did not have lymph node metastasis, and it is important to determine whether additional treatment is indicated after sufficiently considering other factors in addition to depth of SM invasion, such as whether other risk factors for lymph node metastasis are present, the physical and social background of the patient, and the patient’s wishes. Because budding was demonstrated to be an important risk factor for lymph node metastases in the project study by the

JSCCR, additional intestinal resection has been added to the list of factors that should be considered in this revised edition. None of the guidelines in other countries include depth of invasion or budding as criteria for additional treatment.

CQ-2: Endoscopic resection of cM carcinomas and cSM carcinomas with a maximum diameter of 2 cm or greater

Recommendation: Category B

- Accurate preoperative endoscopic diagnosis is essential, and whether resection by EMR, piecemeal EMR, or ESD is indicated is determined after taking the operator’s skill in performing endoscopic resection into consideration.

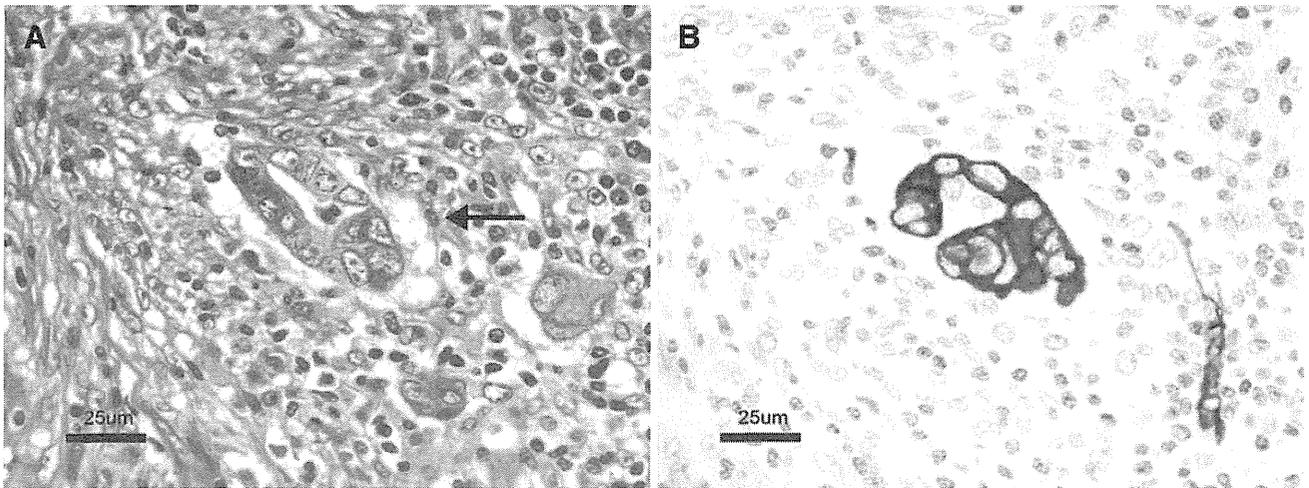


Fig. 14 Space formed by artifacts during preparation of the specimen (*arrow* in **a**). **a** A cancer cell nest is visible in the interstitial space. **b** Double staining for cytokeratin and D2-40. The interstitial space is D2-40-negative

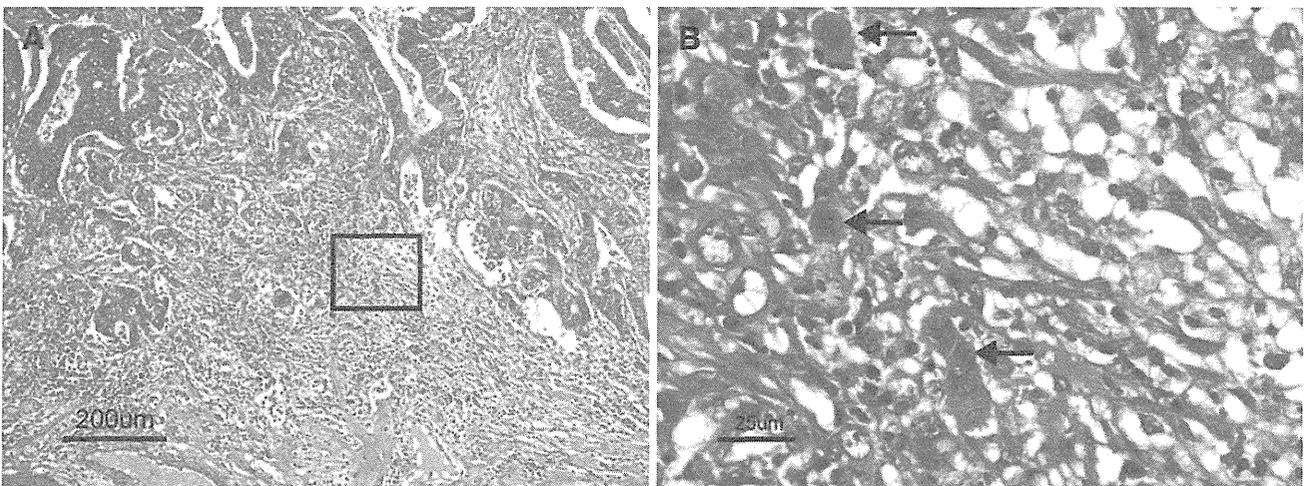


Fig. 15 Budding (*arrows* in **b**). **a** A cancer cell nest consisting of 1 or less than 5 cells that has infiltrated the interstitium at the invasive margin of the cancer is seen. **b** is the square area in **a**

Table 11 Depth of invasion of sm cancer and lymph node metastasis (modified from [80])

sm invasion distance (µm)	Pedunculated		Nonpedunculated	
	Number of lesions	n (+) (%)	Number of lesions	n (+) (%)
Head invasion	53	3 (5.7)		
0 < X < 500	10	0 (0)	65	0 (0)
500 ≤ X < 1,000	7	0 (0)	58	0 (0)
1,000 ≤ X < 1,500	11	1 (9.1)	52	6 (11.5)
1,500 ≤ X < 2,000	7	1 (14.3)	82	10 (12.2)
2,000 ≤ X < 2,500	10	1 (10.0)	84	13 (15.5)
2,500 ≤ X < 3,000	4	0 (0)	71	8 (11.3)
3,000 ≤ X < 3,500	9	2 (22.2)	72	5 (6.9)
3,500 ≤ X	30	2 (6.7)	240	35 (14.6)

The lymph node metastasis rate of patients with a depth of invasion of 1,000 µm or above was 12.5%

All 3 lymph node metastasis-positive patients with head invasion were ly positive

Side Memo 1

- Method for measuring depth of SM invasion (Fig. 11):
 - When it is possible to identify or estimate the location of the muscularis mucosae, depth of SM invasion is measured from the lower border of the muscularis mucosae of the lesion, regardless of the macroscopic type.
 - When it is not possible to identify or estimate the location of the muscularis mucosae, the depth of SM invasion is measured from the surface of the lesion. The phrase “possible to identify or to estimate” means that there is no “deformity” (i.e., disarray, dissection, rupture, fragmentation, etc.) of the muscularis mucosae as a result of SM invasion. If a deformed muscularis mucosa is used as the baseline of the measurement, the depth of SM invasion may be underestimated. Although judging whether there is a “deformity” is not always straightforward, if a desmoplastic reaction is present around the muscularis mucosae, it is assumed to be “deformed.”
 - For pedunculated lesions with a tangled muscularis mucosae, depth of SM invasion is measured as the distance between the point of deepest invasion and the reference line, which is defined as the boundary between the tumor head and the stalk (the boundary between the tumor area and the non-tumor area in the mucosa). Invasion by pedunculated lesions that is limited to within the head is defined as “head invasion.”
- Method for assessing vascular invasion (Figs. 12, 13, 14):
 - Attention to arteries is a key factor in assessing venous invasion. Venous invasion is highly likely when a circular, semicircular, or oblong cancer cell nest with regular margins is located in the vicinity of an artery and distant from the main lesion. If such a cancer cell nest is surrounded by venous wall structures (such as internal elastic membrane or perivascular smooth muscle), it can be concluded to represent venous invasion. However, the venous wall structures are often displaced or obliterated by the cancer cell nest, and it is difficult to recognize in hematoxylin and eosin stained sections.
 - The presence of cancer cells and cancer cell nests in the interstitial space suggests lymphatic invasion. A space filled with lymph and lymphocytes is especially likely to be a lymph vessel. When endothelial cells are identified around the space, the space can be concluded to represent a lymph vessel. However, it is often difficult to identify endothelial cells in specimens

stained with hematoxylin and eosin, and spaces may be artifacts created during the process of preparing the specimen.

- As stated above, evaluation of vascular invasion, which is an important indicator for determining treatment strategies for SM cancer, is often difficult in hematoxylin and eosin stained specimens. Special staining methods are useful for evaluating vascular invasion, such as elastica van Gieson staining or Victoria blue staining for venous invasion, and D2-40 immunostaining for lymphatic invasion.

- Method for assessing tumor budding (Fig. 15):

[Definition of tumor budding] [79]

A cancer cell nest consisting of 1 or less than 5 cells that infiltrates the interstitium at the invasive margin of the cancer.

[Grade of budding]

After selecting one field where budding is the most intensive, the number of buddings is counted in a field measuring 0.785 mm² observed through a 20× objective lens (WHK 10× ocular lens). Depending on the number of buddings, the grade of budding is defined as follows:

- Grade 1: 0–4
- Grade 2: 5–9
- Grade 3: 10 or more

- The lymph node metastasis rate associated with grade 2/3 tumors is significantly higher than that associated with grade 1 tumors. A multi-center study conducted by the Budding Investigation Project Committee (2005–) of the JSCCR in which grade 1 was defined as “low grade” and grade 2/3 as “high grade” showed that high grade is an independent predictor of lymph node metastasis.

CQ-3: Laparoscopic surgery for colorectal cancer

Recommendation: Category B

- Since laparoscopic surgery requires surgical skills that are different from those required for open abdominal surgery, and an understanding of regional anatomy is essential for laparoscopic surgery, the indication criteria should be determined depending on the skills of the surgical team.

Laparoscopic surgery is suitable for D2, D1 or D0 resection of colon and RS cancer, and is well indicated for the treatment of cStage 0 to cStage I disease. Because laparoscopic colectomy with D3 dissection is difficult, whether it is indicated for patients with cStage II to cStage III

disease should be determined after carefully considering the skills of the surgical team. Laparoscopic surgery is also difficult in patients with transverse colon cancer, in severely obese patients, and in patients with severe adhesions. The efficacy and safety of laparoscopic surgery for rectal cancer has not been sufficiently established.

CQ-4: Resection of the primary tumor in patients with unresectable distant metastases

Recommendation: Category B

- The initial resection of the primary tumor should be determined based on the performance status of each patient, such as the symptoms caused by the primary tumor, the status of distant metastases, and the patient's general condition. Resection of the primary tumor is often desirable when a patient has symptoms caused by the primary tumor that cannot be well controlled by other therapies, if the patient is sufficiently able to tolerate surgery, and the resection can be accomplished with acceptable morbidity.

CQ-5: Resection of peritoneal metastases (carcinomatous peritonitis)

Recommendation: Category C

- If patients with localized peritoneal dissemination (P1, P2) have no other unresectable distant metastases and resection will not result in excessive invasion, it is preferable to resect the disseminated tumors at the same time as the resection of the primary tumor.

CQ-6: Surgical treatment for local recurrence of rectal cancer

Recommendation: Category B

- Resection should be considered for local recurrence of rectal cancer when R0 resection is considered possible.

CQ-7: Resection in patients with liver and lung metastases

Recommendation: Category C

- The efficacy of resection in patients who have liver and lung metastases at the same time has been shown, and thus resection should be considered for patients with resectable liver and lung metastases.

However, there are insufficient data to determine the indication criteria for surgery. It is necessary to obtain

informed consent after informing the patient of the rather low cure rate and the absence of outcome predictors.

CQ-8: Adjuvant chemotherapy after curative resection of liver metastases

Recommendation: Category B

- The efficacy of adjuvant chemotherapy after hepatectomy has not been established. It is desirable to investigate its efficacy in clinical trials.

CQ-9: Preoperative chemotherapy for resectable liver metastases

Recommendation: Category B

- The safety of preoperative chemotherapy for resectable liver metastases has not been established. It should be evaluated in properly designed clinical trials.

CQ-10: Chemotherapy for unresectable liver metastases

Recommendation: Category B

- Hepatectomy should be considered for liver metastases that have become resectable after successful chemotherapy.

No clear difference has been observed between hepatic arterial infusion therapy and systemic chemotherapy in terms of the prolongation of survival time of patients with unresectable liver metastases.

CQ-11: Postoperative adjuvant chemotherapy and age

Recommendation: Category A

- Even in patients 70 years old or older, postoperative adjuvant chemotherapy can be performed if their PS is good, if the function of major organs is adequate, and if there are no complications that may be a risk for performing chemotherapy.

CQ-12: Postoperative adjuvant chemotherapy for stage II colorectal cancer

Recommendation: Category A

- The usefulness of postoperative adjuvant chemotherapy for stage II colorectal cancer has not been proven, and it is not appropriate to routinely administer adjuvant chemotherapy to all patients with stage II colorectal cancer.

CQ-13: Duration of postoperative adjuvant chemotherapy

Recommendation: Category A

- Although no definitive conclusion regarding the duration of postoperative adjuvant chemotherapy has been reached, the current standard duration of treatment by 5-FU-based adjuvant chemotherapy is 6 months.

CQ-14: Oxaliplatin (L-OHP) in postoperative adjuvant chemotherapy

Recommendation: Category A

- In August 2009, L-OHP was approved for postoperative adjuvant chemotherapy in Japan. When selecting target patients, the indication should be determined after obtaining sufficient informed consent regarding adverse events and medical care costs as well as the expected additional benefit in terms of survival time.

CQ-15: Molecular target drugs for secondary treatment

Recommendation: Category B

- It is desirable to use bevacizumab as secondary treatment in patients who can be treated with bevacizumab and have not received it as primary treatment. There is no clear evidence supporting the optimal dose in this situation (5 or 10 mg/kg) [44, 49].

CQ-16: KRAS gene mutations and anti-EGFR antibody drugs

Recommendation: Category A

- The usefulness of anti-EGFR antibody drugs has been reported in metastatic colorectal cancer without KRAS gene mutations [38–41, 47, 53, 55, 85–90].

Side Memo 2

- Anti-EGFR antibody drugs and EGFR immunostaining

Since most clinical research on cetuximab has been conducted on EGFR-positive patients, insurance coverage is limited to EGFR-positive patients. On the other hand, most clinical research on panitumumab has also been conducted on EGFR-positive patients, and evidence in regard to EGFR-negative patients is insufficient, but insurance coverage has been restricted to EGFR-positive patients. A recent report showed that there is no relationship between

the effect of anti-EGFR antibody drugs and the level of EGFR expression assessed by immunostaining [91].

- CPT-11 and UGT1A1 genetic polymorphism

SN-38 is an active metabolite of CPT-11 and the UGT1A1 gene encodes an intrahepatic metabolizing enzyme which converts the active form SN-38 to the inactive form SN-38 G. In patients who are double heterozygotes for *6 and *28 or homozygotes for *6 or *28 of the UGT1A1 gene, the glucuronic acid conjugation capacity of UGT1A1 is known to be decreased and the metabolism of SN-38 to be delayed, and serious adverse drug reactions such as neutropenia may occur as a result. It is especially desirable to test for a UGT1A1 genetic polymorphism before administering CPT-11 to patients with a high serum bilirubin level, elderly patients, patients whose general condition is poor (e.g., PS2), and patients in whom severe toxicity (especially neutropenia) developed after the last administration of CPT-11. On the other hand, because CPT-11 toxicity cannot be predicted with certainty on the basis of the presence of a UGT1A1 genetic polymorphism alone, it is essential to monitor the patient's general condition during treatment and manage adverse drug reactions carefully regardless of whether a genetic polymorphism is detected.

CQ-17: Significance of preoperative chemoradiotherapy for rectal cancer

Recommendation: Category C

- Preoperative chemoradiotherapy is standard treatment for rectal cancer in Europe and the United States. However, there is insufficient evidence in support of its efficacy and safety in Japan, and it needs to be evaluated in properly designed clinical trials.

CQ-18: Chemoradiotherapy for unresectable locally advanced and locally recurrent rectal cancer

Recommendation: Category C

- The indication for chemoradiotherapy aiming at complete cure by R0 resection will also be considered for locally advanced or locally recurrent, unresectable rectal cancer.

CQ-19: Significance of surveillance after surgery of colorectal cancer

19A: Diagnosis of recurrence

Recommendation: Category A

- Early detection of recurrence has been shown to contribute to an improvement in outcome, and

postoperative surveillance examinations should be performed regularly. However, an optimal surveillance protocol incorporating the health economical point of view has not been sufficiently established.

19B: Multiple cancer

Recommendation: Category B

- With the exception of hereditary colorectal cancer, a past medical history of colorectal cancer has not been demonstrated to be a risk factor for the development of cancer in other organs, and it is unnecessary to incorporate special surveillance for multiple cancer into the surveillance performed after curative surgery for colorectal cancer.

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がん登録からみたがん診療ガイドラインの普及効果に関する研究
－診療動向と治療成績の変化－

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研究要旨

婦人科悪性腫瘍の治療ガイドラインは日本婦人科腫瘍学会が中心となって2002年に作成に着手した。子宮頸癌、子宮体がん（子宮肉腫、絨毛癌を含む）、卵巣がん（胚細胞性腫瘍、性索間質腫瘍、卵管癌、腹膜癌、境界悪性腫瘍を含む）の婦人科の3大がんを3年から4年おきに順次改訂している。平成24年度は、子宮体がんの2013年版（第3版）と卵巣がんの2014年版（第4版）の改定作業を進めている。さらに、これまでに作成したガイドラインに対する客観的な評価と検証に着手し、本年8月に8名の委員から構成される委員会を新たに設置した。

A. 研究目的

子宮体がんならびに卵巣がんの治療ガイドラインは、日本で行われる子宮体がんならびに卵巣がんの治療において、より良い方法を選択するための一つの基準を示し、現在までに集積しているそれらの根拠を記すことにある。両治療ガイドライン作成の目的は、現時点で適正と考えられる治療法を示すこと、治療レベルの施設間差を少なくすること、治療の安全性の恒常と予後の改善をはかること、適正な治療を行うことによって患者の心身の負担や経済的負担を軽減すること、患者と医療従事者の相互理解に役立つこと、などである。

「子宮体癌治療ガイドライン」初版（2006年版）の3年後に改訂された第2版（2009年版）では、「子宮体がん治療ガイドライン」に名称を変更し、子宮体がんの特殊組織型ならびに癌肉腫・肉腫を新設し、また推奨グレードCを2段階に変更し、C1とC2に区分した。今回の改訂では、手術術式に関して骨盤・傍大動脈リンパ節郭清術とセンチネルリンパ節生検、内視鏡下手術、術後療法、手術後のホルモン補充療法について最近の知見を踏まえて更新する。また、絨毛性疾患として侵入奇胎および絨毛癌を新たに加える。

「卵巣がん治療ガイドライン」は、2004年版を初版とし、2007年、2010年に改訂を行ったが、今回は Clinical Question (CQ) 形成に一新する。その結果として、国内の治療に関する意見が最新のデータをもとにさらに集約されることを目的とする。

加えて、日本婦人科腫瘍学会が刊行してきた3つのガイドラインのそれぞれの内容の客観的な評価を目的に、8名の婦人科腫瘍専門医により構成される委員会を設置する。

B. 研究方法

1. 子宮体がん治療ガイドラインならびに卵巣がん治療ガイドラインの改訂

これまでの作成行程に準じて、日本婦人科腫瘍学会の会員を中心に「作成委員会」と「評価委員会」を独立して設け、両者の十分な検討を経て原案を作成する。その後、日本産科婦人科学会、日本癌治療学会、婦人科悪性腫瘍研究機構（JGOG）、日本産婦人科医学会、日本放射線腫瘍医学学会、日本病理学会などの関係する諸学会や諸団体の意見を取り入れて最終案をまとめ、本学会会員に公開しコンセンサスを得た後、学会の承認を経て最終版とする。

本ガイドラインに採用したエビデンスの多くは欧米、一部は本邦における臨床試験から得られた内容である。しかし、欧米と日本との様々な背景の違いから、欧米における質の高いエビデンスの中には本邦では受け入れ難いものもある。逆に、日本で一般に行われている治療内容が欧米のものとは異なることもある。このような事例では、国内における現時点でのコンセンサスを優先させている推奨内容もある。

2. 既刊の治療ガイドラインの評価

日本婦人科腫瘍学会では刊行してきた3つのガイドラインについて、既に、ガイドライン作成委員会が主導し、初版の卵巣がん 2004 年版ならびに子宮体癌 2006 年版に関するアンケート調査を会員に対して行い、機関誌上で報告した。今回は、新たに設置した「婦人科小班会議」が主導し、最新の子宮頸癌 2011 年版の検証のためにアンケート調査を行う。

(倫理面への配慮)

本研究に関係するすべての研究者は研究対象者に対する人権擁護の配慮としてヘルシンキ宣言に従うほか、臨床試験に関する倫理指針に準拠することとした。

C. 研究結果

1. 子宮体がん治療ガイドライン 2013 年版の作成

ガイドライン作成委員会として、4名の小委員長、公募の中から28名の委員が選任され、委員長、副委員長、4人の幹事を加え、第1回の改訂委員会を2011年11月24日に開催し、改訂のポイントについて議論した。第2回、3回、4回改訂委員会を、2011年12月17日、2012年5月1日、7月18日に行い、原案の作成と修正を重ねた。さらに、第52回日本婦人科腫瘍学会(2012年7月21日)において、新たな対象疾患となった絨毛性疾患についてコンセンサスマーティングを行った。

今後、評価委員による原案の評価、第5回改訂委員会、パブリックコメントの聴取を経て、第54回日本婦人科腫瘍学会(2013年7月開催)において最終案についてのコンセンサスマーティングを予定し、第6回改訂委員会の後に2013年11月の発刊を予定している。

内容は、第1章：ガイドライン総説、第2章：初回治療(特殊組織型を含む)、第3章：術後療法(特殊組織型を含む)、第4章：治療後の経過観

察、第5章：進行・再発癌の治療、第6章：妊孕能温存(子宮内膜異型増殖症・高分化型類内膜型腺癌)、第7章：癌肉腫・肉腫の治療、第8章：絨毛性疾患の治療、第9章：資料集から構成する予定である。

2. 卵巣がん治療ガイドライン 2014 年版の作成

ガイドライン作成委員会として、4名の小委員長、94名の公募の中から39名の委員を選任した。委員長、副委員長、4人の幹事を加えた第1回の改訂委員会を2012年11月22日に開催し、改訂のポイント、特にCQ形式への変更を中心に検討を行う。

3. 子宮頸癌治療ガイドライン 2011 年版の評価

最新の治療ガイドラインの評価として、第54回日本婦人科腫瘍学会(2013年7月開催)において、参加者(約千名)に対して、利用状況、使用目的、有用性を中心にアンケート調査を行う。

D. 考察

1. 子宮体がん治療ガイドライン 2013 年版

FIGO国際進行期分類が2009年に改訂され、それをもとに「子宮体癌取扱い規約第3版」が2012年に発刊された。今回のガイドライン改訂では、この分類と規約に準じたことが既刊のものとは大きく異なる。

2009年の第2版以降に国内外で議論が重ねられてきた子宮体がんの手術術式では、特に骨盤・傍大動脈リンパ節郭清術の意義とセンチネルリンパ節生検の評価について解説を行った。また、国際的に導入・応用が急速に進む内視鏡下手術による婦人科悪性腫瘍手術に関して、現在関連5団体で協議が進められている婦人科内視鏡悪性腫瘍手術の指針を反映する形で適応を述べている。術後療法では、術後化学療法やホルモン療法の有効性、放射線療法の適応を明確にし、さらに、本邦の「ホルモン補充療法(HRT)ガイドライン」が2012年に改訂されたことを踏まえ、手術後のHRTの推奨の可否を示している。また、「絨毛性疾患取扱い規約」が2011年に改訂されたことを受けて、子宮体部に好発する侵入奇胎および絨毛癌の治療について新たに加えた。以上の主な改訂によって、わずか4年間で国際的に大きく変化している子宮体がんの治療の最良の指針を明ら

かにする充実したガイドラインになると期待される。一方、前回の改訂の中心となった特殊組織型は各章に盛り込み、子宮温存については、別章であった子宮内膜異型増殖症に高分化型類内膜型腺癌を併せて妊孕性温存として示すことで、より理解し易い内容になっている。

2. 卵巣がん治療ガイドライン 2014年版

婦人科悪性腫瘍のガイドラインの中で、2004年に最初に発刊された卵巣がん治療ガイドラインは、国際的にも治療の動向が激しく変化する疾患であることを受けて、改訂毎に内容が一新されてきた。その一方で、日本癌治療学会がん診療ガイドライン評価委員会からは、他の2つのガイドラインと異なってCQ形式ではないことが指摘されてきた。これを受けて、今回の第4版ではCQ形式に改めることで、治療指針がより明確になるものと確信している。

3. 子宮頸癌治療ガイドライン 2011年版

日本婦人科腫瘍学会は、患者さんと家族向けのガイドラインの解説を目的として、3つのガイドラインを一体にまとめた「患者さんとご家族のための子宮頸がん・子宮体がん・卵巣がん治療ガイドラインの解説」を2010年に刊行した。作成作業を始めて10年を経過する中で、治療を行う側と受ける側の治療指針のツールは整った。今後、3つのガイドラインの内容や公表に関する評価は、今後の改訂に大きな影響を与え、その結果として最適な治療指針に近づいていくものと考えられる。過去2回にわたって卵巣がんと子宮体癌の初版ガイドラインに関するアンケートが行われたが、その後時間も経過した。その中で、来夏に行う予定である子宮頸癌ガイドラインに対するアンケート調査の結果がわれわれのガイドラインの今後の方向性を示すことになる。

E. 結論

3大婦人科がんの治療ガイドラインは、子宮頸癌が2版、子宮体がんが2版、卵巣がんが3版と版を重ね、子宮体がんと卵巣がんでは新たに改定作業を行っている。これまで、医学的に有効で広く認知された最新の治療を反映させることに尽力してきた。今後は作成を担当する日本婦人科腫瘍学会の内外から客観的に評価と検証を行うことで、増加する婦人科悪性腫瘍の治療の

均霑化に繋がるものと期待される。

F. 健康危険情報

なし

G. 研究発表

1. 論文発表

なし

2. 学会発表

八重樫伸生，片渕秀隆：子宮体がん治療ガイドライン・コンセンサスマーケティング. 第52回日本婦人科腫瘍学会. 東京, 2012年7月21日

H. 知的財産権の出願・登録状況

1. 特許取得

なし

2. 実用新案登録

なし

3. その他

なし

がん登録からみたがん診療ガイドラインの普及効果に関する研究
—診療動向と治療成績の変化—

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研究要旨

日本泌尿器科学会を中心としたがん登録事業とがん診療のガイドライン作成に基づく診療動向および予後調査の結果、前立腺癌におけるStage Migrationが認められた。

A. 研究目的

日本泌尿器科学会を中心としたがん登録事業とがん診療のガイドライン作成は、1980年に開始された膀胱がん登録と膀胱癌取り扱い規約初版の刊行に始まり、2001年には前立腺がん、2002年に腎盂尿管がん、2005年に精巣腫瘍の登録が開始。以後各臓器において5年毎の登録と予後調査が行われており、診療動向と治療成績の変化が検討されてきた。一方で各種がん取扱い規約の改訂およびがん診療ガイドラインの改訂も随時行われている。本研究では、過去に行われたがん登録に基づく診療動向および予後調査結果について報告する。

B. 研究方法

泌尿器がん登録の集計に基づいた泌尿器癌診療の傾向、予後調査の結果を解析。膀胱癌については約4000例、前立腺癌については11385例を集計。

(倫理面への配慮)

2006年、個人情報を含むデータの提出が問題となったため、全国泌尿器がん登録の「研究計画書」が国立がんセンターの倫理審査委員会において承認をうけ、「疫学研究に関する倫理指針」を全国の専門医教育施設へ送付した。以後、初診症例登録時に予後も入力できるようプログラムを作成し、確定診断の5年後を目処に登録を依頼することとした。

C. 研究結果

2000年に登録された4529例の前立腺癌症例のうち、明らかに転移を有する症例は20%以上であり、2671例の限局性前立腺癌のうち、約46%にホルモン単独療法が行われていた¹⁾。

2004年に登録された11385例のうち、転移を有する症例は11.6%であり、2010年の調査時における全生存率は89.7%、癌特異的生存率は94.8%であった。8424例の限局性前立腺癌のうち、初期治療としてホルモン単独療法が約40%において行われており、欧米のデータと比較して多い傾向にあった²⁾。

1991年から2001年にかけて登録された3237例の膀胱癌のうち1, 3, 5年無再発生存率はそれぞれ77.0%, 61.3%, そして52.8%であった⁵⁾。

1991年から2001年にかけて登録された1919例のT1膀胱癌のうち3年以上の経過観察で76例の癌死が確認された。癌死のリスクは非乳頭状腫瘍、尿細胞診陽性、腫瘍径3cm以上が有意なリスクであった⁴⁾。

D. 考察

前立腺癌については2001～2004年の登録約32000例について、疫学の推移を柱として、集計・解析中である。

腎盂尿管癌については2005年登録の538症例について集計・解析中。

精巣腫瘍については2005年・2008年登録の774症例について集計・解析中である。

さらに2012年に腎がん登録開始のためのワーキンググループが発足した。来年度にがん登録を予定している。

E. 結論

日本泌尿器科学会によるがん登録は膀胱癌に始まり、前立腺癌、腎盂尿管癌、精巣腫瘍、腎癌と続いて行われている。各種泌尿器癌におけるStage Migrationや5年生存率の経年変化の検討が必要である。

G. 研究発表

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H. 知的財産権の出願・登録状況：特になし

Clinical Data

Clinicopathological statistics on registered prostate cancer patients in Japan: 2000 report from the Japanese Urological Association

CANCER REGISTRATION COMMITTEE OF THE JAPANESE UROLOGICAL ASSOCIATION

Abstract

Background: The purpose of the present paper was to investigate etiology, diagnosis, initial treatment, pathological findings and final outcomes for prostate cancer in Japan.

Methods: From 2001, the Japanese Urological Association initiated computer-based registration of prostate cancer patients in Japan to estimate etiology, diagnosis, initial planned treatment, pathological findings and final outcome.

Results: A total of 173 institutions responded and 4529 patients who were diagnosed with prostate cancer in 2000 were registered. In the first year, background factors, diagnostic procedures and initially planned treatment were recorded. The analysis of these registered cases is presented here. Nearly 30% of the cases demonstrated <10 ng/mL of prostate specific antigen. The six-core biopsy was the most commonly used procedure. The clinical T staging distribution was as follows: T1c, 20.3%; T2a, 21.8%; T2b, 17.3%; T3a, 15.8%; T3b, 11.0%; and T4, 8%. More than 70% of cases were diagnosed as M0. Hormone therapy alone was the initial treatment plan in more than half of the cases.

Conclusion: This is the first report on prostate cancer patients in Japan based on multi-institutional registration. Pathological findings and final outcome will be surveyed later by the Japanese Urological Association. After 5 years, adopted treatment, pathological results and final outcome will be registered.

Key words epidemiology, Japan, neoplasm, prostate.

Introduction

Prostate cancer is known around the world as a disease of elderly men. Parkin *et al.* reported that three-quarters of cases occur in men over 65 years of age.¹ In Japan, although the incidence of prostate cancer has been much less than in American and European countries, it has been sharply rising during the last two decades, a trend also observed in other Asian countries. Even before the introduction of prostate specific antigen (PSA) testing in the early 1990s, incidence rates had been rising in

many countries.^{1–5} Changes from traditional Japanese to more Western lifestyles and nutritional habits have been implicated in the increase in the incidence of prostate cancer in Japan.³ In the early 1990s, the PSA test contributed to the earlier diagnosis of prostate cancer, which is also reflected in the increased incidence. Now, in Japan as in other developed countries, prostate cancer is a large and growing public health problem whose risk factors are essentially unknown.

The precise nature of this problem differs from one country to another because of the wide range of national incidence and, to a much lesser degree, survival profiles that have been reported.^{1,5–8} Recently, however, Nakata *et al.*⁴ reported that the mortality rate of prostate cancer patients in Japan has been increasing as rapidly as the incidence, while in North America the mortality rate has actually declined even in the face of rising incidence.⁹

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The Japanese Urological Association (JUA) and the Japanese Society of Pathology revised the 2nd edition of *General Rule for Clinical and Pathological Studies on Prostate Cancer* to the 3rd edition in 2001¹⁰ and, in accordance with this new edition, initiated a study to estimate the etiology, diagnosis, initial treatment, pathological findings and final outcomes for prostate cancer in Japan by employing computer-based registration of prostate cancer patients from institutions all over Japan. The registration program has been established by the members of committee for revision of *General Rule for Clinical and Pathological Studies on Prostate Cancer*. Here we report the background data at diagnosis from the initial registration of 4529 patients who were diagnosed pathologically with prostate cancer in 2000.

Methods

Using a CD-ROM program developed by the members of committee for revision of *General Rule for Clinical and Pathological Studies on Prostate Cancer* and the staff of the National Cancer Center, new patients who were diagnosed by pathology to have prostate cancer in 2000 were registered. Age, occupation, race, concomitant malignancy, family history, past history and symptoms were entered as background factors for each prostate cancer patient. The findings from digital rectal examination (DRE), imaging, PSA level, number of cores taken by biopsy, number of positive core(s), histology of the biopsy specimen, Gleason score, 5th tumor, nodes, metastases (TNM) classification (5th edition), diagnostic process and initial treatment plan were also entered. The collected data were analyzed.

Results

One hundred and seventy-three institutions responded and 4529 patients who were diagnosed with prostate cancer in 2000 were registered. Approximately 14 000 new prostate cancer patients were estimated in Japan this year;⁹ therefore, approximately 30% of total cases were covered by this registry.

Background data

The age distribution of patients is summarized in Figure 1. More than one-quarter of all patients were 70–74 years old, and three-quarters were 60–79 years old. The ethnic distribution was as follows: Japanese, 99.56%; non-Japanese Mongolians, 0.29%; and Caucasian, 0.13%. Only 71 patients (1.57%) had a family

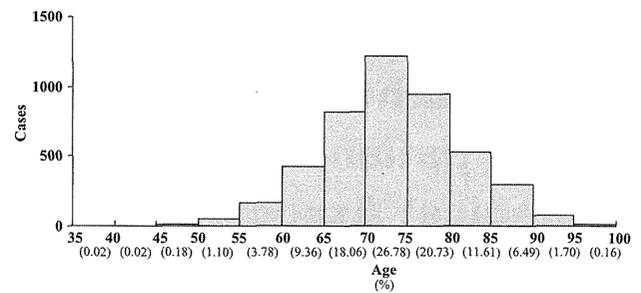


Fig. 1 Age distribution of prostate cancer newly diagnosed in 2000 and registered. Registered cases were divided into 5-year age groups as indicated. Bars indicate the number of cases equal to and above the age on the left lower corner and below the age on the right lower corner of each bar. The numbers below each bar indicate the percentage of cases in each age group among all registered cases.

Table 1 Findings of local imaging study

	<i>n</i>	(%)
Not visible	1255	27.71
Confirmed within prostate	1580	34.89
Extra-capsule	732	16.16
Invades adjacent structure	685	15.12
Uncertain	277	6.12
Total	4529	100.00

history of prostate cancer in either their father (0.66%), brother (0.82%), or uncle (0.09%). Common occupations of the registered patients were the following: retired (61.29%), office clerks or associate professionals (8.06%), corporate or general managers (6.93%), agricultural, forestry, or fishery workers (6.71%), and professionals or technicians (6.62%). A total of 520 patients (11.48%) had a history of other malignancies.

Initial evaluation

Of all the patients, 71.08% (3219 cases) presented with some symptoms and 339 cases (7.49% of all and 35.17% of metastatic disease) presented with symptoms from metastases.

The most commonly used staging modalities were transrectal ultrasonography (TRUS; 78.32%) and bone scan (73.53%), followed by computed tomography (CT; 66.75%) and magnetic resonance imaging (MRI; 42.77%). The findings from local imaging studies are summarized in Table 1. As expected, local imaging studies yielded better sensitivity (66.17% produced a positive finding) than DRE (58.29% true-positives; Table 2).

Table 2 Findings of digital rectal examination

	<i>n</i>	(%)
Not palpable	1706	37.67
One lobe	1090	24.07
Both lobe	760	16.78
Extra-capsule	481	10.62
Seminal vesicle invasion	113	2.50
Extra-prostate	196	4.33
Uncertain	18.3	4.04
Total	4529	100.00

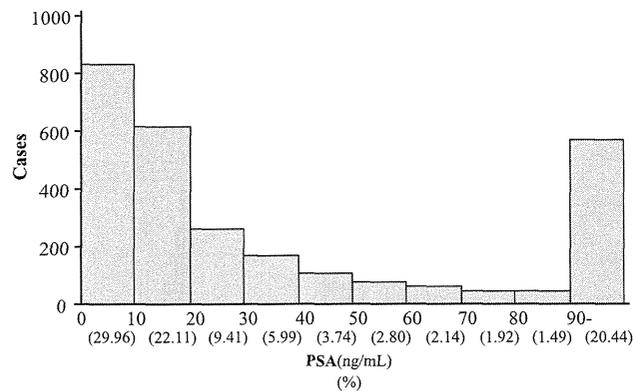


Fig. 2 Distribution of prostate specific antigen (PSA) value of registered cases. Registered cases were divided into groups of PSA value by 10 ng/mL as indicated. The PSA value was measured by Tandem-R and includes all Tandem-R compatible kits, such as *E*-test Tosoh, Chemilumi ACS-PSA, Shifalite PSA and Lumipulse PSA. Bars indicate the number of cases equal to and above the value on the left lower corner and below the value on the right lower corner of each bar. Cases with PSA ≥ 90 ng/mL were counted as a single group. The numbers below each bar indicate the percentage of cases in each group among all registered cases.

The PSA level distribution is summarized in Figure 2. Nearly 30% of prostate cancer cases diagnosed in 2000 demonstrated a PSA value of <10 ng/mL.

A summary of the biopsy statistics is shown in Tables 3–5 and Figure 3. Because the same number of cores is usually taken from each lobe, the 5th, 7th, and 9th core samples are supposed to be additional targeted biopsies of suspicious lesions (Table 3). The percentage of biopsies yielding all positive cores was higher for the 6-core than for the 8-core biopsy (Fig. 3). However, the percentage of biopsies yielding only one positive core was higher for the 8-core procedure. A total of 99.8% of tumors were determined pathologically to be adenocarcinoma, followed by neuroendocrine tumors (0.1%). Moderately differentiated adenocarcinoma (43.5%) was

Table 3 Number of adopted biopsy cores

Core(s)	<i>n</i>	(%)
1	5	0.12
2	93	2.30
3	52	1.28
4	264	6.52
5	90	2.22
6	2128	52.52
7	282	6.96
8	616	15.20
9	90	2.22
≥ 10	432	10.66
Total	4052	100

Uncertain, 168 patients.

Table 4 Primary Gleason grade

Gleason grade	<i>n</i>	(%)
1	376	8.30
2	541	11.90
3	1155	25.50
4	695	15.30
5	308	6.80
Uncertain	1454	32.10
Total	4529	100

Table 5 Secondary Gleason grade

Gleason grade	<i>n</i>	(%)
1	251	5.50
2	552	12.20
3	1020	22.50
4	780	17.20
5	312	6.90
Uncertain	1614	35.60
Total	4529	100

the most common differentiation state found in this population, followed by well-differentiated (31.3%) and poorly differentiated adenocarcinomas (20.6%). Gleason grade classification is summarized in Tables 4,5; grade 3 was found to be the most common grade in both primary and secondary dominant tumors.

Initial staging

Clinical T stage of this population is summarized in Figure 4. The clinical T staging distribution is as follows: T1c, 20.3%; T2a, 21.8%; T2b, 17.3%; T3a, 15.8%; T3b, 11.0%; and T4, 8%. Regionally limited lymph node metastases examined mainly by CT were found in 501 cases (11.06%), and 3569 cases

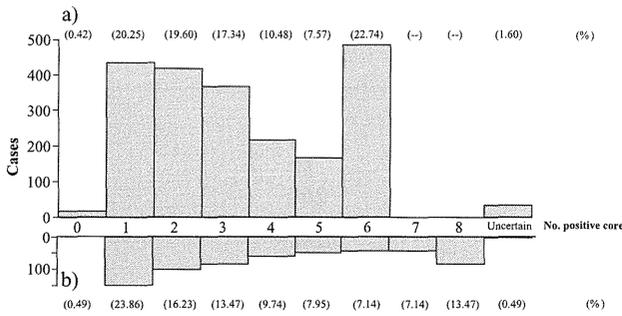


Fig. 3 Number of cancer-positive cores in (a) 6-core biopsy ($n = 2128$) and (b) 8-core biopsy ($n = 616$). Registered cases were divided into groups by number of cancer-positive cores as indicated. Bars indicate the number of cases in each group. The percentage of cases in each group among each subgroup of 6- or 8-core biopsy is indicated over or below the bars.

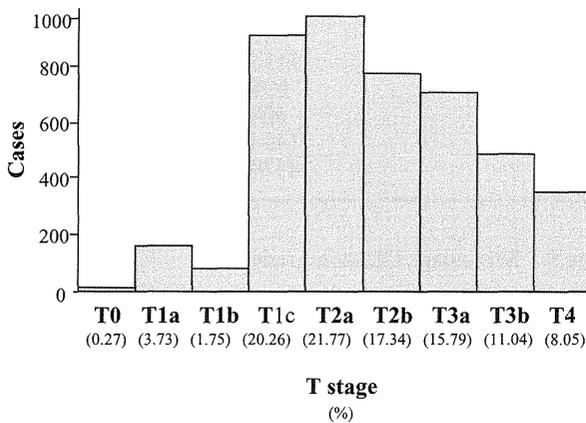


Fig. 4 Distribution of local staging (T staging). Registered cases were divided into groups by local staging as indicated according to the 1997 International Union Against Cancer (UICC) tumor, nodes, metastases (TNM) classification. Bars indicate the number of patients for each T stage. The numbers below each bar indicate the percentage of cases in each age group among all registered cases.

(78.80%) were diagnosed as negative lymph node metastasis.

Distant metastases are detailed in Table 6. More than 70% of patients were negative for distant metastasis.

Initial treatment strategies

Selected plans are summarized in Figure 5. Hormonal therapy alone was chosen for more than half of the cases. Prostatectomy with or without hormonal therapy was planned for 27.4% (1240 cases). Irradiation with or without hormonal therapy was not very common (8.1%). For cases of T1c to T3N0M0 (2671 cases total),

Table 6 M stage

M stage	<i>n</i>	(%)
M0	3243	71.61
M1a	40	0.88
M1b	861	19.01
M1c	63	1.39
MX	322	7.11
Total	4529	100

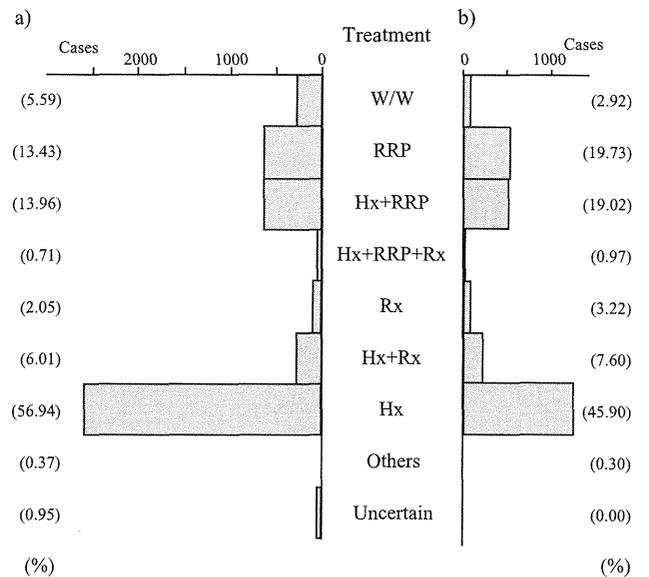


Fig. 5 Initial treatment plan for (a) all registered cases ($n = 4529$) and (b) cases of T1c to T3 without lymph node or distant metastases ($n = 2671$). Registered cases were divided into groups by initial treatment plan, which includes each treatment modality and appropriate combinations, as indicated. W/W, watchful waiting; RRP, retropublic radical prostatectomy; Hx, hormonal therapy; Rx, irradiation. Bars indicate the number of cases in each group. The numbers below each bar indicate the percentage of cases in each group among all registered cases or the subgroup of patient at stage T1c to T3 without lymph node or distant metastases.

45.90% (1226 cases) were scheduled to undergo hormonal therapy without any other additional treatment. Irradiation was not commonly advised for this group (10.8%).

Additional data are summarized in Appendix I-IV.

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Appendix

I. General statistics

I.1. Background

I.1.1. Races

Race	Number	%
Japanese	4509	99.56
Mongolian (without Japanese)	13	0.29
White	6	0.13
Uncertain	1	0.02
Total	4529	100

I.1.3. Occupation

Occupation	Number	%
Service workers	101	2.23
Transportal and postal related workers	63	1.39
Corporate and general managers	314	6.93
Craft, related trades workers and elementary occupations	165	3.64
Mining labourers	8	0.18
Office clerks and associate professionals	365	8.06
Professionals and technicians	300	6.62
Agricultural, forestry and fishery workers	304	6.71
Sales workers	119	2.63
Protective services workers	14	0.31
Others or retired	1002	22.12
Uncertain	1774	39.17
Total	4529	100

I.2. Symptoms

I.2.1. Urological

Symptoms	Number	%
+	3219	71.08
-	1273	28.11
Uncertain	37	0.82
Total	4529	100

I.3. Staging method and findings

I.3.1. Modality of image study

Number	% in all cases	
CT	3023	66.75
MRI	1937	42.77
Bone scan	3330	73.53
TRUS	3547	78.32

I.1.2. Family history of prostate cancer

	Number	%
Father	30	0.66
Brother	37	0.82
Uncle	4	0.09
Total	71	1.57

I.1.4. Distribution of organs of concomitant malignancy

Organ	Number
Kidney	33
Urothelial	111
Testis	2
Penile	3
Head and neck	34
Lung	50
Esophageal	10
Stomach	107
Colon	120
Liver and gall bladder	19
Pancreas	9
Skin	6
Hematological	8
Sarcoma	3
Breast	1
Uncertain and other	4
Total	520
Negative	4022

I.2.2. Metastatic

Symptoms	Number	%
+	339	7.49
-	4137	91.34
Uncertain	53	1.17
Total	4529	100