patients under 12 months of age, 73 were detected through mass screening at 6 months of age. In all cases, the status of MYCN amplification was determined by Southern blotting, quantitative polymerase chain reaction (PCR), and fluorescent in situ hybridization (FISH) [5]. According to the International Neuroblastoma Staging System (INSS) [6], there were 79 (64%) patients with stages 1, 2, and 4S; 16 (13%) with stage 3; and 28 (23%) with stage 4. Seventeen (14%) patients had MYCN amplification. The 5-year survival rate was 76%.

Survival curves for each category were constructed using the Kaplan–Meier method and then statistically evaluated by the log-rank test.

Results

Treatment and outcomes of the patients less than 12 months of age

In principle, since 1994, the protocol of the Japanese Infantile Neuroblastoma Study Group has been applied to patients under 12 months of age [7, 8]. This protocol consists of the following: An initial tumor extirpation is performed for localized resectable neuroblastomas; then, if no MYCN amplification is detected, postoperative chemotherapy is not administered. A biopsy is taken of an unresectable neuroblastoma, followed by mild chemotherapy if no MYCN amplification is detected in the tumor. Usually, no second-look operation is performed for residual tumors that decrease in size with chemotherapy after a biopsy, if the biology, including the MYCN gene status, is favorable. If MYCN amplification is detected in the tumor, intensive chemotherapy with a decrease in dose according to age is given, with or without tumor extirpation.

Of our 82 patients under 12 months of age, 70 (85%) had stage 1, 2, or 4S and 2 (2%) had MYCN amplification; the 5-year survival rate was 97% (Table 1). There were no significant differences in the survival rates between the 59 patients who underwent complete resection and the 23 who underwent incomplete resection (Fig. 1). Moreover, of the 59 patients who underwent complete resection, there were no significant differences in the survival rates of the 38 who received chemotherapy and the 21 who did not. All 23 patients who underwent incomplete resection of the tumor received postoperative chemotherapy, and all these patients survived (Table 2).

Of the nine patients with neuroblastoma detected clinically, and not through mass screening, four had stage 4S, three had stage 1, and two had stage 4 disease. One patient with stage 4S disease had MYCN amplification. Seven of these nine patients underwent complete resection of the primary tumor. Six patients with stage 4 or 4S received mild chemotherapy after operation. Three patients with stage 1 received no postoperative chemotherapy after complete resection of primary tumor. The patient who had stage 4S disease with MYCN amplification died of the disease.

Surgical complications developed in five patients: postoperative bleeding in one, renal atrophy in three, and adhesive intestinal obstruction in one. One patient with partial resection of a stage 2 tumor suffered postoperative bleeding; two patients with complete resection of a stage 1 tumor and one patient with partial resection of a stage 3 tumor suffered renal atrophy; and one patient with complete resection of a stage 1 tumor suffered adhesive intestinal obstruction. All five patients with a surgical complication were alive without disease at the time of writing.

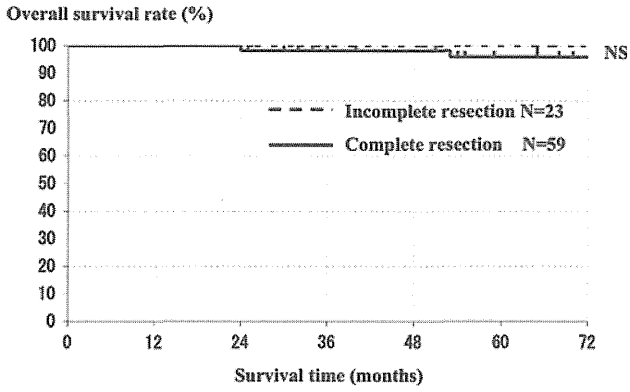

Fig. 1 Correlation between tumor resection and prognosis in 82 neuroblastoma patients less than 1 year of age. *NS* not significant

Table 1 Characteristics of 82 patients less than 12 months old with neuroblastoma

	No. of patients
Stages 1, 2, 4S	70 (85%)
Stages 3, 4	12
No MYCN amplification	80 (98%)
With MYCN amplification	2
5-year survival rate	97%

Table 2 Outcome of the 82 patients less than 12 months old with neuroblastoma based on chemotherapy and type of resection

Chemotherapy	Tumor resection	Survival
Received ($n = 61$)	CR ($n = 38$)	35 (92%)
	ICR ($n = 23$)	23 (100%)
Not received ($n = 21$)	CR ($n = 21$)	21 (100%)
	ICR ($n = 0$)	

CR complete resection, *ICR* incomplete resection

Treatment and outcomes of the patients aged 12 months or older with advanced neuroblastoma

In principle, since 1985, the protocol of the Japan Study Group for Advanced Neuroblastoma (JANB) has been applied to patients aged 12 months or older with advanced neuroblastomas [9, 10]. This protocol consists of the following: First, a biopsy is taken of the tumor, followed by intensive induction chemotherapy based on the MYCN gene status. A second-look operation is performed for residual tumors that decreased in size following the induction chemotherapy after biopsy. The second-look operation usually involves complete resection of the primary tumor, avoiding injury to the surrounding organs and major vessels. Enlarged lymph nodes are usually resected with sampling the surrounding lymph nodes, but systematic lymphadenectomy is not performed. If the second-look operation involves the complete resection of the tumor, then postoperative localized external-beam radiation (2–30 Gy) is given, followed by high-dose chemotherapy with stem cell transplantation. If the second-look operation involves incomplete resection of the tumor, postoperative localized external-beam radiation (20–30 Gy) is given, followed by consolidation chemotherapy.

Regarding the degree of resection of the primary tumor, macroscopic complete resection is defined as complete resection without systematic lymphadenectomy at the initial diagnosis or at the second-look operation after induction chemotherapy, and surgical intervention for the primary tumor, such as a biopsy only, partial resection, and subtotal resection, is defined as incomplete resection.

Of our 41 patients more than 1 year old with neuroblastomas, 32 (78%) had stage 3 and 4 disease and 15 (36%) showed MYCN amplification. The 5-year survival rate of these 41 patients was 42% (Table 3). The 86% 5-year survival rate of the 9 patients with stage 1 and 2 disease was significantly better than the 30% 5-year survival rate of the 32 patients with stage 3 and 4 disease ($P < 0.05$). Moreover, the 25% 5-year survival rate of the 15 patients with MYCN amplification was significantly worse than the 53% 5-year survival rate of the 26 patients without MYCN amplification ($P < 0.05$) (Fig. 2). Of 9 patients with early (stage 1 or 2) disease and no MYCN amplification, 5 with stage 1 underwent initial complete resection of the tumor, and 4 with stage 2 underwent initial incomplete resection of the tumor. All except 1 of the 8 patients with stage 1 disease underwent postoperative mild chemotherapy. One of these patients died of another disease.

Table 3 Clinical characteristics of the 41 patients aged 12 months or older with neuroblastoma

Clinical characteristics	No. of patients
Stage	
Stage 1, 2, and 4S	9
Stage 3 and 4	32 (78%)
MYCN amplification	
No amplification	26
Amplification	15 (36%)
5-year survival rate	42%

There was no significant difference in 5-year survival rate between the 19 (46%) patients who underwent complete resection and the 22 (38%) who underwent incomplete resection (Fig. 3). Furthermore, the survival rate of the 32 patients with stage 3 and 4 disease did not differ significantly between the 11 patients who underwent complete resection and the 21 who underwent incomplete resection.

No local recurrence was observed in the ten patients over 1 year old with stage 4 disease who underwent complete resection of the primary tumor without systematic lymphadenectomy and local irradiation after 1994, although four of these patients died of metastatic recurrence (Table 4). Seven of these ten patients underwent stem cell transplantation (SCT); however, SCT was not associated with their outcome. No major surgical complications occurred.

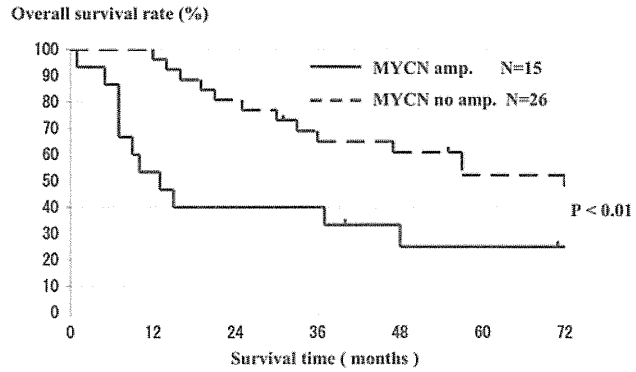

Fig. 2 Correlation between MYCN amplification (amp.) and prognosis in 41 neuroblastoma patients aged 12 months or older

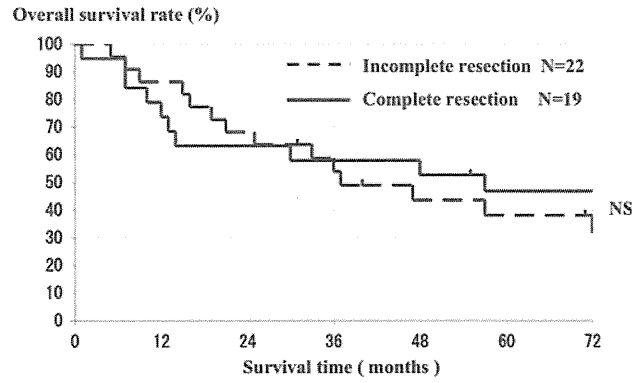

Fig. 3 Correlation between tumor resection and prognosis in 41 neuroblastoma patients aged 12 months or older

Table 4 Clinical course of the ten patients with stage 4 neuroblastoma who underwent complete resection of the primary tumor (1994–2004)

Patient no	Initial metastatic site	MYCN amplification	Local radiation	Local recurrence	Metastatic recurrence	Outcome
1	N, B, E, bm	no amp.	30 Gy	(−)	B	Died
2	N, B, E, bm	amp.	30 Gy	(−)	(−)	Alive 13 years after surgery
3	N, bm	amp.	30 Gy	(−)	(−)	Alive 10 years after surgery
4	N, bm	amp.	30 Gy	(−)	B, bm	Died
5	B	no amp.	30 Gy	(−)	B	Died
6	B, bm	amp.	30 Gy	(−)	N, B, bm	Died
7	B, bm, H	no amp.	30 Gy	(−)	(−)	Alive 6 years after surgery
8	B, bm, H	no amp.	18 Gy	(−)	(−)	Alive 6 years after surgery
9	N, bm	amp.	24 Gy	(−)	(−)	Alive 5 years after surgery
10	B, bm	amp.	18 Gy	(−)	(−)	Alive 5 years after surgery

N lymph node, *B* bone, *E* orbit, *bm* bone marrow, *amp.* amplification, *no amp.* no amplification

Discussion

The prognosis of patients with neuroblastoma tends to vary greatly, based on clinical prognostic factors, such as age and stage, and biological prognostic factors, such as MYCN amplification, DNA ploidy, and chromosome 1p deletion [11]. Thus, it is important to select the optimal therapy, including surgical intervention, according to the characteristics of these tumors [12]. This study is the experience of one institution between 1985 and 2004, during which time the treatment regimen for patients under 12 months of age with neuroblastomas and that for patients aged 12 months or over with advanced neuroblastomas did not change. Other investigators recently reported that 18 months of age is more preferable for risk assessment. In this study, the protocol of the Japanese Infantile Neuroblastoma Study Group was applied for patients less than 12 months of age with neuroblastomas, and the protocol of the Japan Study Group for Advanced Neuroblastoma (JANB) was applied for patients aged 12 months or older with advanced neuroblastomas. Therefore, investigating the borderline of age for risk group classification was not suitable for the analysis in the present study.

The majority of infant neuroblastomas are localized tumors with low-grade malignancy [13]. In particular, neuroblastomas detected by mass screening include spontaneously regressing tumors [14]. In the present series of 82 patients under 12 months of age, the outcome of infant neuroblastomas was excellent, regardless of whether they underwent complete or incomplete resection of the tumor. Furthermore, the outcome of patients who underwent complete resection of the tumor was excellent, regardless of whether they received postoperative chemotherapy. We could not compare patients who underwent initial extirpation with those who did not, because biopsies were performed for all unresectable neuroblastomas, followed by mild chemotherapy. Although complete resection might be unnecessary for infantile neuroblastoma, the majority of which have favorable biology, performing initial tumor extirpation might avoid the need chemotherapy or irradiation.

In the present study, of nine patients whose disease was detected clinically and not through mass screening, only one patient who had stage 4S disease with MYCN amplification died of the disease. Irrespective of mass screening, most patients under 12 months of age had a good prognosis. It is clear that MYCN gene amplification was a powerful prognostic factor, even for infantile neuroblastoma [8].

In the present study, all five major surgical complications occurred in the patients with localized neuroblastoma (stages 1, 2, and 3). Recently, in an effort to establish a new risk-adapted preoperative neuroblastoma staging system, the International Neuroblastoma Risk Group (INRG) task force proposed the use of surgical risk factors (SRFs) to classify localized neuroblastomas [15]. SRFs were defined by objective and subjective radiologic imaging characteristics thought to be associated with an increased risk of surgical complications. These radiologic criteria are known as "image-defined risk factors" (IDRF) [16]. In a retrospective radiologic review of the five patients with surgical complication, all those who suffered postoperative renal atrophy had a positive IDRF. The Japan Neuroblastoma Study Group (JNBSG) proposed guidelines for surgical intervention for localized neuroblastoma based on the IDRF and began observational study of the treatment for low-risk neuroblastomas in 2010.

The role of surgery in the treatment of advanced neuroblastoma in patients 12 months or older remains controversial. La Quaglia et al. [17] reported that gross total resection improved the survival of 39 patients with stage IV neuroblastoma. Conversely, Adkins et al. [18] reported that complete resection was of little benefit for high-risk

neuroblastomas treated by CCG-3891. Kuroda et al. [19] found that intensive surgery with intraoperative radiation therapy dramatically increased local eradication and improved the outcome of patients even if they had advanced neuroblastomas with MYCN amplification. On the other hand, Castel et al. [20] found that delayed surgery after chemotherapy contributes to the good control of stage IV disease, although the final outcome of these patients was determined more by metastatic relapses than by the degree of resection. Kaneko et al. and Kubota et al. reported that systemic extensive surgery for advanced or metastatic neuroblastoma is no longer required if therapy supplemented with intensive pre- and postoperative chemotherapy is given [4, 21]. In the present study, the clinical stage and tumor biology of advanced neuroblastoma in patients aged 12 months or older was associated with the overall survival rate. The degree of tumor resection did not correlate significantly with the overall survival rate. In this study, the second-look operation was conservative tumor resection of the primary tumor, avoiding the injury to the surrounding organs and major vessels, and systematic lymphadenectomy was not performed. Therefore, we could not examine the complications of surgery and the delay in administering intensive chemotherapy resulting from major surgery. No major complications occurred after the second-look operation for the advanced neuroblastomas in patients aged more than 1 year old in this study, and we avoided a delay in intensive chemotherapy after the operation. Furthermore, complete resection of the primary tumor without systematic lymphadenectomy and localized external-beam radiation prevented local recurrence; however, the outcome of patients depended on metastatic recurrence. These results indicate that the main treatment for advanced neuroblastoma in patients aged 12 months or older is systemic chemotherapy, and that extirpation of the primary tumor without major surgery might prevent local recurrence, when combined with irradiation therapy.

In the JNBSG, two clinical phase II studies for high-risk neuroblastoma were begun in 2008 and completed in 2010. The guidelines for surgical intervention in these clinical studies recommend complete resection of the primary tumor without systematic lymphadenectomy, and localized irradiation. The long-term outcomes, including late complications, revealed by these clinical studies will be interesting.

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The prognostic significance of blastemal predominant histology in initially resected Wilms' tumors: A report from the Study Group for Pediatric Solid Tumors in the Kyushu Area, Japan

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Key words:
Wilms' tumor;
Nephroblastoma;
SIOP;
NWTS;
Blastemal predominant

Abstract

Background and Purpose: The strategy used to treat pediatric renal tumors in Japan is based on the Japanese Wilms' Tumor Study (JWiTS) protocol, which was based on the National Wilms' Tumor Study (NWTS)-5 regimen. The regimen is characterized by an initial radical operation, followed by adjuvant chemotherapy and radiotherapy. Concerning the histological classification, a new classification based on the International Society of Pediatric Oncology (SIOP) classification was used beginning in 2008. The main points of revision are that the "blastemal predominant type" was classified as an independent category in the Wilms' tumor subtypes. The purpose of this study was to analyze the biological characteristics from the standpoint of the newly established histological classification.

Materials and Methods: From 1971 to 2005, 174 cases of Wilms' tumors treated with an initial operation followed by adjuvant therapy were re-evaluated by the new histological classification. Histologically, all these materials showed no secondary changes associated with adjuvant therapy.

Results: According to the new classification, Wilms' tumors were classified into four subtypes, including the mixed type (n = 112), epithelial type (n = 17), mesenchymal type (n = 15), and blastemal predominant type (n = 26). The 5 year overall survival rates were as follows; mixed type (90.1%), epithelial type (100%), mesenchymal type (93.3%), and blastemal predominant type (65.4%).

Conclusion: The patients with blastemal predominant tumors demonstrated a significantly worse prognosis compared with those of other subtypes. The treatment strategy of blastemal predominant category should be distinguished from the other favorable subtypes.

Wilms' tumor is one of the most common malignant neoplasms in children. There are two typical treatment strategies. One strategy described by the National Wilms'

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Tumor Study (NWTS; now part of the Children's Oncology Group, COG), recommends an initial radical operation, followed by adjuvant chemotherapy and radiotherapy. In the NWTS pathological system, two different histological classifications (favorable or unfavorable) have been defined. On the other hand, in Europe, the International Society of Pediatric Oncology (SIOP), advocates the efficacy of preoperative chemotherapy. In the recent SIOP pathology system (SIOP 93–01, SIOP 2001), three risk groups (low, intermediate, high) were defined and are based on the percentage of overall necrosis and the predominant cell type in the residual viable cells [1-3].

In Japan, the strategy for treating Wilms' tumors had been fundamentally based on the NWTS regimen until the Japanese Wilms' Tumor Study (JWiTS) was established in 1996 [4]. The original pathological evaluation system was based on the NWTS classification and was used in Japan until 2008. However, since new knowledge had become available at that time, a new classification system based on the SIOP pathological classification was implemented in 2008. The main revisions in a new pathological classification system in Japan were as follows:

1. The Japanese pathological system, which is the classification of all pediatric renal tumors, including Wilms' tumors, was reformed extensively based on the classification of the SIOP pathological system.
2. Malignant rhabdoid tumor of the kidney (MRTK) and clear cell sarcoma of the kidney (CCSK), which had been classified as nephroblastoma according to the old classification system, were classified into independent categories.
3. A new category for metanephric tumors was added.
4. The classification for pediatric renal cell carcinoma was changed to correlate with molecular genetic features.
5. The findings of specific gene abnormalities were considered to complement the decision on the pathological diagnosis.

By using this new classification system, the blastemal predominant type of nephroblastoma (Fig. 1) was classified as an independent subtype from other subtypes (mixed type, epithelial type, mesenchymal type). While in the SIOP reports, the outcome of patients with the blastemal predominant type had a poor prognosis [2], in the NWTS reports, blastemal predominance was not categorized in an unfavorable histology group, and there have been no reports referring to a worse prognosis for this group.

For many years in Japan the strategy had been based on the NWTS strategy, and surgical specimens not affected by preoperative chemotherapy could be collected for various studies. This made it possible to evaluate tumors with blastemal predominance unaffected by preoperative chemotherapy.

Therefore, in this study, blastemal predominant type nephroblastomas were retrospectively assessed by a new pathological classification based on the SIOP system, the treatment strategy based on the NWTS protocol, and outcomes were evaluated.

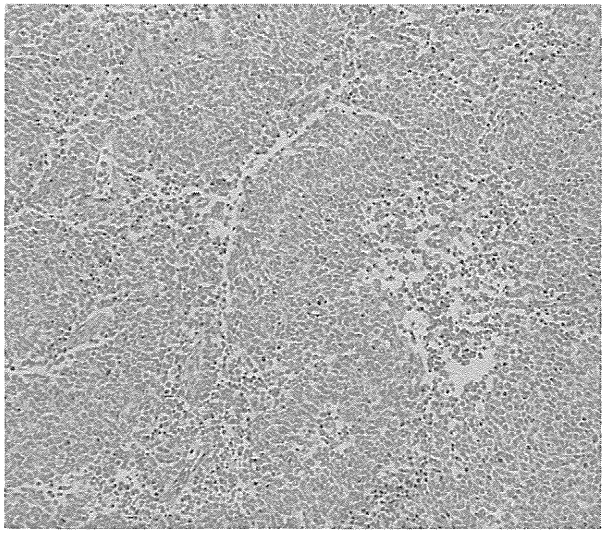

Fig. 1 The histological features of the blastemal predominant type. Proliferation of oval to polygonal tumor cells having hyperchromatic nuclei and scant cytoplasm, arranged in sheets.

1. Materials and methods

1.1. Patients

In the Kyushu area in Japan, the registration system for pediatric solid malignant tumors was established in 1971 [5]. A total of 259 pediatric renal tumor were registered between 1971 and 2005. All of these cases were treated by either complete resection or incomplete resection before chemotherapy. Among these cases, 174 Wilms' tumors, for which prognosis was confirmed by follow-up survey, were extracted for this study. The study was performed according to the Ethical Guidelines for Clinical Research published by the Ministry of Health, Labor, and Welfare of Japan on July 30, 2003.

1.2. Methods

The histological features of the tumors were classified according to the newly established Japanese pathology classification (Table 1) based on the original SIOP classification (Table 2). Although none of the patients had received preoperative chemotherapy in this study (which is different from the SIOP guidelines), the subtypes of Wilms' tumor were defined as follows (based on the SIOP system). The tumors were classified as epithelial, blastemal, or mesenchymal when each subtype occupied more than 2/3 of the tumor. When predominance was not seen, the subtype was defined as mixed. The mesenchymal subtype is

Table 1 The Japanese histological classification (2008).

- ●Nephroblastoma
  - –Mixed
  - –Epithelial
  - –Mesenchymal
  - –Blastemal predominant
- ●Nephroblastoma
(Special type and related lesion)
  - –Anaplasia
  - –Nephrogenic rest
  - –CPDN
  - –Bilateral nephroblastoma
  - –Extrarenal nephroblastoma
- ●Metanephric tumors
- ●CMN
- ●CCSK
- ●RTK
- ●RCC
- ●Miscellaneous tumors

CPDN: cystic partially differentiated nephroblastoma.
CMN: congenital mesoblastic nephroma.
CCSK: clear cell sarcoma of the kidney.
RTK: rhabdoid tumor of the kidney.
RCC: renal cell carcinoma.

equivalent to the stromal subtype in the SIOP classification. The clinical data including patient age, stage and outcome were analyzed. The staging system in this study was defined according to the Japanese Staging System, which is similar to that used in the NWTS system [4]. The statistical analysis of the differences in the 5 year overall survival and 5 year event free survival were calculated by the Kaplan-Meier method. Comparisons of the prognostic impact of each factor including age, stage (early stage: stage 1 and 2, advanced stage: stage 3, 4 and 5), overall survival and event free survival between the blastemal predominant type and other subtypes were performed using the chi-square test and log-rank test.

Table 2 The revised SIOP working classification (2001).

- ●Low risk tumors
  - –CMN
  - –CPDN
  - –Nephroblastoma-completely necrotic (following preoperative chemotherapy)
- ●Intermediate risk tumor
  - –Nephroblastoma epithelial type
  - –Nephroblastoma stromal type
  - –Nephroblastoma mixed type
  - –Nephroblastoma regressive type
  - –Nephroblastoma focal anaplasia type
- ●High risk tumors
  - –Nephroblastoma blastemal type
  - –Nephroblastoma diffuse anaplasia type
  - –Clear cell sarcoma of the kidney
  - –Rhabdoid tumor of the kidney

2. Results

There were 112 cases of mixed type, 17 cases of epithelial type, 15 cases of mesenchymal (stromal) type, and 26 cases of the blastemal predominant type of Wilms' tumor that were defined during the re-classification. Anaplasia was recognized in four cases. (Table 3). The affected age was slightly older in the blastemal predominant type group than other groups (mixed, epithelial, mesenchymal type), however, the difference was not significant.

The treatment strategies of all cases were identical to that of the NWTS with respect to the drugs administered.

With regard to prognosis, the 5 year overall survival was as follows; mixed type (90.1%), epithelial type (100%), mesenchymal type (93.3%) and blastemal predominant type (65.4%) (Table 3 and Fig. 2). On the other hand, the 5 year event free survival rates were as follows; mixed type (87.5%), epithelial type (100%), mesenchymal type (80.0%), and blastemal predominant type (52.6%). The outcome of the patients with blastemal predominant type Wilms' tumors was significantly worse than patients with other subtypes (Table 3).

Concerning the tumor histology and stage, the number of patients diagnosed with each stage was stage 1 > stage 2 > stage 3 and stage 4 for all types except the blastemal predominant type. In the blastemal predominant type, there were more stage 2 cases than any other and then the order was stage 3 > stage 4 and stage 1. Statistically, blastemal predominant type showed more significant dominance in the advanced stages than those of other subtypes (Table 4). Of particular importance, there were deaths in patients at all of the different stages (Table 5). The relapsed cases had various patterns of recurrence, including both local recurrence and distant metastasis (generally to lung or liver), and a definite tendency was not identified.

Table 3 The clinical data according to the newly established Japanese histological classification.

Histology	Number	Age (months)	5OS (%)	5EFS (%)
Mixed	112	30.4 ± 22.2	90.1 *	87.5 *
Epithelial	17	28.2 ± 28.7	100 *	100 *
Mesenchymal	15	29.6 ± 40.8	93.3 *	80.0 *
Blastemal	26	33.4 ± 30.6	65.4	52.6
Anaplasia	4	20.8 ± 11.9	50.0	50.0

The average of age distribution showed no significant difference.
OS: overall survival.
EFS: event free survival.
* Blastemal predominant type showed significantly poorer prognosis ($p < 0.05$) than mixed, epithelial, and mesenchymal subtypes.

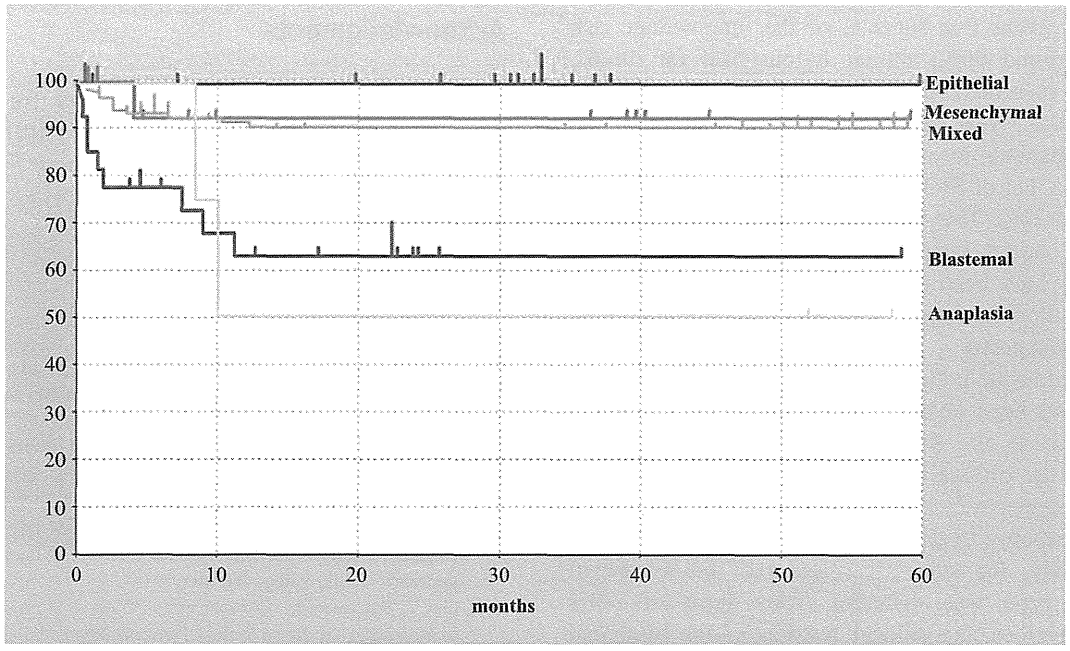

Fig. 2 The five year overall survival of the patients with Wilms' tumors.

3. Discussion

It is well known that the pathology of Wilms' tumors demonstrates tri-phasic features, namely, blastemal, epithelial, and stromal components. Concerning the NWTS protocol, which is based on the pathological findings obtained from initially resected tumor specimens, the tumors are generally considered to have favorable histology (nephroblastoma without anaplasia) or unfavorable histology (anaplasia). In the SIOP protocol, the classification depends on the pathological findings associated with necrosis or the amount of viable cells remaining after preoperative chemotherapy. Since blastemal predominant features had been considered a high risk pathological finding, intensive chemotherapy was administered to these patients. However, there has been no report that a predominancy of blastemal cells contributes to a poor prognosis based on the NWTS system.

The prognostic superiority or inferiority with regard to the initial operation recommended by the NWTS system or the preoperative chemotherapy recommended by the SIOP has not yet been demonstrated [6], and the characteristics of blastemal cells are still largely unknown.

In one SIOP-9/GPOH study, the relapse rate of the blastemal predominant type was 31.1% [7]. A recent report of SIOP/GPOH trials and studies showed that the relapse rate of Wilms' tumors was 12%, and that of the blastemal predominant type was 21.1%, whereas that of the epithelial type was 3.5% and that of the stromal type was 2.3% [8].

Fortunately, since the most past cases had not undergone preoperative chemotherapy in Japan, the samples were easily extracted for reappraising the features of blastemal predominance. For this reason, the Japanese specimens are suitable for original evaluations of the impact of blastemal predominance on prognosis.

In the SIOP 93–01 working classification, three risk classifications (low, intermediate, high) after preoperative chemotherapy were defined. Namely, epithelial, stromal, and mixed types were classified in the intermediate risk group, and the blastemal type was classified in the high risk group [9,10]. Compared to the SIOP 93–01 working classification,

Table 4 The stage distribution.

Histology	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5	p value
Mixed	40.0%	36.3%	8.9%	13.3%	6.5%	<0.01
Epithelial	82.3%	11.7%	0%	0%	6.0%	<0.01
Mesenchymal	46.7%	20.0%	6.7%	6.7%	20.0%	<0.01
Blastemal	15.4%	42.3%	19.2%	15.4%	7.7%	
Anaplasia	50.0%	25.0%	25.0%	0%	0%	<0.01

P value < 0.01 indicates a significant difference concerning the distribution between early stage (stage 1 and 2), and advanced stage (stage 3, 4, and 5).

Table 5 The outcomes of the blastemal predominant type.

	Stage 1	Stage 2	Stage 3	Stage 4	Stage 5
Number (5) (%)	4 (15.4%)	11 (42.3%)	5 (19.2%)	4 (15.4%)	2 (7.7%)
Alive (Relapse−)	3	9	1	0	0
Alive (Relapse+)	0	0	1	2	1
Died of disease	1	2	3	2	1

the four year event free survival of the intermediate risk group was around 90%, similar to our data for mixed, epithelial and mesenchymal.

However, the 5-year event free survival in the blastemal predominant patients in our study was only 52.6%, which was inferior to that of SIOP 93–01 data showing a survival rate of around 70%. This may have been influenced by the NWTS-based initial radical resection, since some cases might actually have been excluded from the category of the blastemal predominant type if preoperative chemotherapy had been administered.

With regard to the biology of the blastemal predominant type, there have been several controversial reports, where a good response to the therapy was observed. Beckwith reported that the diffuse blastemal pattern was associated with marked aggressiveness, but with a high survival rate due to the good response to chemotherapy [11].

In our study, the stage distribution of the blastemal predominant type was different from those of other subtypes. Therefore, the clinical features of the blastemal predominant type are distinct from other subtypes. However, we think this group should be classified in still greater detail, because some cases may be included that show a good response to initial treatment, and might be able to excluded from this category. These groups should be analyzed from other standpoints, such as based on genetic factors.

There have been several reports of genetic studies of Wilms' tumors [12,13]. Beckwith-Wiedemann syndrome and perilobar nephrogenic rests have a significant relationship, and the associated tumors commonly show a blastemal predominant histology [14]. The NWTS-5 reported that loss of heterozygosity (LOH) for chromosomes 16q and 1p is predictive of an adverse outcome [15]. Recently, WTX on the X chromosome was found to be inactivated in up to one-third of Wilms' tumors [16]. However, there have been no reports demonstrating the association between these genetic loci and the blastemal histology.

Based on the analysis in this study, a unique and purely histological evaluation was performed with untreated specimens, and new knowledge was acquired. In Japan, we had followed the NWTS based regimen for a long time. However, our data demonstrates that the prognosis for the blastemal predominant type is worse than other subtypes of Wilms' tumor. There have been no similar reports from NWTS evaluating blastemal predominance.

Based on further analyses including additional prognostic factors, a new strategy should be developed for blastemal predominant Wilms' tumors.

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Trends in 'Cure' Fraction from Colorectal Cancer by Age and Tumour Stage Between 1975 and 2000, Using Population-based Data, Osaka, Japan

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Since the 1960s, Japan has experienced a striking increase in the incidence of colorectal cancer, now the second most common cancer in the country. Meanwhile, the management of colorectal cancer has changed dramatically with the implementation of, for example, screening, endoscopy and adjuvant chemotherapy. It is therefore of interest to monitor the long-term trends in population 'cure' in Japan. We analysed 33 885 colorectal cancer cases diagnosed between 1975 and 2000 in Osaka. We applied the multivariable mixture cure model to estimate cure fraction and median survival time (MST) for 'uncured' patients, by sex, age, stage, period at diagnosis and subsite. For colon cancer, the cure fraction increased by about 25%, while MST for the uncured was prolonged from 8 to 12 months. The cure fraction was 5% higher in men than in women, while MST was similar in both. The cure fraction also increased for localized and regional tumours. For rectal cancer, the cure fraction increased by about 25–30%, but remained lower than for colon cancer. From the late 1970s, the cure fraction for colorectal cancer increased dramatically due to better management of detection and care for colorectal cancer. This improvement was obtained at the cost of shorter MST for uncured patients.

Key words: cure – cancer registry – cancer survival – colorectal cancer

BACKGROUND

As a result of a rapid increase in incidence for four decades since the mid-1960s, colorectal cancer has become one of the most common cancers in Japan (1,2). Colorectal cancer incidence in Japan is one of the highest worldwide (3) due to rapid diet transformations (4,5) and colorectal cancer is a predominant public health burden. In the past three decades, there have been important changes in the management of colorectal cancer in Japan: a programme of mass screening by the faecal occult blood test was initiated in 1992, while several major improvements in treatment have also been implemented.

Prognosis for colorectal cancer has improved significantly in Japan, with 5-year survival at about 30% in the early 1970s and 55% in early 2000 (6). However, this single indicator may be insufficient to completely and accurately reflect the numerous, important changes in managing colorectal cancer patients and to identify the remaining weaknesses. We aimed to assess the impact of these changes by monitoring the trends in population 'cure' of colorectal cancer in

Osaka, Japan. The effect of age and tumour stage at diagnosis on these trends was also examined.

METHODS

Data Sources

We analysed 21 032 colon (ICD-10 code: C18) and 12 757 rectal (C19–C20) cancer cases diagnosed and registered in the population-based cancer registry of Osaka Prefecture between 1975 and 2000. The Osaka cancer registry regularly receives death certificates for patients resident in the Osaka Prefecture at the time of their death. Furthermore, the vital status of the patients who are known as still alive 5 and 10 years after diagnosis was checked using the city-level residence registries. Those cases diagnosed from 1975 to 1995 were followed up for 10 years after their diagnosis, whereas follow-up was limited to 5 years for those diagnosed from 1996 to 2000. We did not include patients of Osaka city (36%) in our analysis, because the vital status of patients in Osaka city diagnosed before 1993 was not recorded. A small proportion of cases were lost to follow-up, 2.2% of the patients diagnosed in 1975–95 (10-year follow-up) and 1.2% of the patients diagnosed in 1996–2000 (5-year follow-up).

Statistical Analysis

Cure Parameters

Within the relative survival framework, population cure is a statistical concept corresponding to the absence of excess mortality among cancer patients in comparison to a similar general population (7). The mortality of this general population, the background mortality, is provided by life tables. Cure models assume that the cancer patients can be split into two groups: the 'cured' group and on top of that, the 'uncured' group for which relative survival function is estimated. Using separate calculations for men and women, and for colon and rectum, we estimated the cure fraction and median survival time (MST) for uncured cases, by the period of diagnosis (1975–80, 1981–85, 1986–90, 1991–95 and 1996–2000), age at diagnosis (15–49, 50–59, 60–69, 70–79 and 80–99), tumour stage at diagnosis (localized, regional and distant metastasis) and, for colon, subsite (left and right colon). We applied a multivariate mixture cure fraction model with a logit link and a Weibull distribution for the survival of the uncured patients. Both Weibull parameters (i.e. shape and scale parameters) were allowed to vary by period, age and stage at diagnosis since proportional excess hazards were unlikely for these variables (8). Background mortality was provided by national life tables for Japan, defined by sex, single year of age and single calendar year.

Missing Data

Tumour stage data were missing for 10% of the colorectal cancer patients and subsite for about 25% of the colon cancer patients (Table 1). Multiple imputation by chained equation (9) was applied to deal with this missing information. The imputation model consisted of multinomial logistic models containing, in addition to tumour stage and subsite (for colon), follow-up time, vital status, period and age at diagnosis, tumour morphology as well as interactions between follow-up time and age and stage. Ten 'completed' data sets were generated with imputed values for the cases with missing information for stage and subsite. Cure parameters were then estimated on the 10 completed data sets using Rubin's rules (10).

Patients with missing stage data were more likely to be older and diagnosed in the earlier calendar periods, while there was very little variation with time among the proportion with missing subsite data (11). The imputed stage was mostly regional metastasis in the early period and then shifted to the localized stage. The imputed subsite was a little more left-side colon. For older patients, survival time for patients missing stage or subsite data was shorter than patients with known stage or subsite.

All data management and analyses were carried out using Stata MP version 11.1 (12).

RESULTS

During the study period, age at diagnosis of colorectal cancer increased. The proportion of patients with localized tumours increased until the mid-1990s while the proportion of both the regional and distant tumours decreased. The pattern of change seems to have reached a plateau in the late 1990s (Table 1).

Although their levels differed in some ways, trends in both cure parameters were very similar for men and women, and for colon and rectum cancers (Tables 2 and 3; Supplementary Figs S1 and S2). Overall, both the cure fraction and the MST for uncured increased during the study period, with a dramatic improvement for the cure fraction. However, the MST for uncured shortened in the early (colon) or late (rectum) 1990s, while the cure fraction did not improve in the late 1990s. Among the patients diagnosed with colon cancer from 1996 to 2000, 62% of men and 58% of women were predicted to be cured of their cancer, with an MST for uncured of just below 1 year. For rectal cancer and both sexes, the cure fraction was about 57% with an MST of slightly less than 18 months.

The overall temporal trends by age group were very similar, with a dramatic increase in cure fraction across all age groups for both cancer sites and sexes. Overall, the cure fraction varied little with age until the age of 80 and over (Tables 2 and 3; Supplementary Figs S3 and S4). For the period 1996–2000, if the MST for uncured reached 12 months or more (colon) and 18 months (rectum) for patients under 70 years old, it remained particularly short for the elderly, lower than 6 months (colon) or around 8 months (rectum).

Table 1. Characteristics of colorectal cancer patients in Osaka (Japan), 1975–2000

	Period of diagnosis											
	1975–80		1981–85		1986–90		1991–95		1996–2000		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Colon												
Men												
Total	879	100.0	1361	100.0	2171	100.0	3496	100.0	3677	100.0	11 584	100.0
Age												
<50	216	24.6	237	17.4	310	14.3	387	11.1	275	7.5	1425	12.3
50–59	189	21.5	339	24.9	599	27.6	928	26.5	771	21.0	2826	24.4
60–69	227	25.8	328	24.1	613	28.2	1173	33.6	1340	36.4	3681	31.8
70–79	208	23.7	348	25.6	487	22.4	723	20.7	905	24.6	2671	23.1
80+	39	4.4	109	8.0	162	7.5	285	8.2	386	10.5	981	8.5
Stage (before imputation)												
Localized	209	28.2	382	31.6	843	43.5	1639	52.9	1647	48.1	4720	45.3
Regional	343	46.2	490	40.6	654	33.7	863	27.8	998	29.1	3348	32.1
Distant	190	25.6	336	27.8	442	22.8	599	19.3	782	22.8	2349	22.5
Missing	137	(15.6)	153	(11.2)	232	(10.7)	395	(11.3)	250	(6.8)	1167	(10.1)
Stage (after imputation)												
Localized	254	28.9	422	31.0	934	43.0	1841	52.7	1757	47.8	5208	45.0
Regional	402	45.8	551	40.5	731	33.7	974	27.9	1069	29.1	3727	32.2
Distant	223	25.3	388	28.5	506	23.3	681	19.5	851	23.1	2649	22.9
Subsite (before imputation)												
Right	301	45.6	421	40.4	604	35.9	911	36.4	1113	39.5	3350	38.5
Left	359	54.4	621	59.6	1077	64.1	1592	63.6	1705	60.5	5354	61.5
Missing	219	(24.9)	319	(23.4)	490	(22.6)	993	(28.4)	859	(23.4)	2880	(24.9)
Subsite (after imputation)												
Right	404	45.9	549	40.4	791	36.4	1278	36.5	1461	39.7	4483	38.7
Left	476	54.1	812	59.6	1380	63.6	2219	63.5	2216	60.3	7101	61.3
Women												
Total	764	100.0	1191	100.0	1815	100.0	2671	100.0	3007	100.0	9448	100.0
Age												
<50	139	18.2	210	17.6	251	13.8	317	11.9	236	7.8	1153	12.2
50–59	143	18.7	244	20.5	414	22.8	589	22.1	598	19.9	1988	21.0
60–69	234	30.6	297	24.9	480	26.4	777	29.1	853	28.4	2641	28.0
70–79	184	24.1	330	27.7	466	25.7	623	23.3	806	26.8	2409	25.5
80+	64	8.4	110	9.2	204	11.2	365	13.7	514	17.1	1257	13.3
Stage (before imputation)												
Localized	156	24.8	322	30.1	587	35.7	1008	42.7	1183	43.0	3256	38.5
Regional	315	51.8	459	52.8	632	51.5	819	49.2	959	52.6	3184	51.4
Distant	159	54.3	287	70.0	426	71.5	532	63.0	610	70.5	2014	67.0
Missing	134	(17.5)	123	(10.3)	170	(9.4)	312	(11.7)	255	(8.5)	994	(10.5)

Continued

Table 1. *Continued*

	Period of diagnosis											
	1975–80		1981–85		1986–90		1991–95		1996–2000		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Stage (after imputation)												
Localized	188	24.6	349	29.3	645	35.5	1132	42.4	1269	42.2	3582	37.9
Regional	384	50.2	516	43.3	701	38.6	926	34.7	1050	34.9	3576	37.9
Distant	193	25.2	326	27.4	470	25.9	613	23.0	689	22.9	2290	24.2
Subsite (before imputation)												
Right	263	47.7	366	40.8	605	42.9	839	43.5	1084	47.8	3157	44.7
Left	288	52.3	531	59.2	804	57.1	1090	56.5	1186	52.2	3899	55.3
Missing	213	(27.9)	294	(24.7)	406	(22.4)	742	(27.8)	737	(24.5)	2392	(25.3)
Subsite (after imputation)												
Right	371	48.6	503	42.3	782	43.1	1163	43.5	1429	47.5	4248	45.0
Left	393	51.4	688	57.7	1033	56.9	1509	56.5	1578	52.5	5200	55.0
Rectum												
Men												
Total	847	100.0	1151	100.0	1588	100.0	2005	100.0	2371	100.0	7962	100.0
Age												
<50	210	24.8	234	20.3	283	17.8	263	13.1	239	10.1	1229	15.4
50–59	189	22.3	278	24.2	466	29.3	590	29.4	643	27.1	2166	27.2
60–69	204	24.1	284	24.7	436	27.5	693	34.6	893	37.7	2510	31.5
70–79	209	24.7	282	24.5	300	18.9	319	15.9	437	18.4	1547	19.4
80+	35	4.1	73	6.3	103	6.5	140	7.0	159	6.7	510	6.4
Stage (before imputation)												
Localized	184	28.0	381	36.7	620	43.6	903	48.1	1016	46.0	3104	43.1
Regional	330	50.2	440	42.4	537	37.7	663	35.3	792	35.9	2762	38.3
Distant	143	21.8	216	20.8	266	18.7	313	16.7	400	18.1	1338	18.6
Missing	190	(22.4)	114	(9.9)	165	(10.4)	126	(6.3)	163	(6.9)	758	(9.5)
Stage (after imputation)												
Localized	241	28.5	420	36.5	688	43.3	950	47.4	1089	45.9	3389	42.6
Regional	422	49.8	488	42.4	602	37.9	708	35.3	847	35.7	3067	38.5
Distant	184	21.7	243	21.1	298	18.8	347	17.3	435	18.3	1506	18.9
Women												
Total	588	100.0	750	100.0	976	100.0	1198	100.0	1283	100.0	4795	100.0
Age												
<50	155	26.4	171	22.8	226	23.2	208	17.4	164	12.8	924	19.3
50–59	108	18.4	155	20.7	241	24.7	290	24.2	301	23.5	1095	22.8
60–69	147	25.0	193	25.7	222	22.7	334	27.9	381	29.7	1277	26.6
70–79	136	23.1	167	22.3	212	21.7	261	21.8	282	22.0	1058	22.1
80+	42	7.1	64	8.5	75	7.7	105	8.8	155	12.1	441	9.2

Continued

Table 1. *Continued*

	Period of diagnosis											
	1975–80		1981–85		1986–90		1991–95		1996–2000		Total	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Stage (before imputation)												
Localized	154	33.5	268	40.3	362	41.8	519	46.5	521	43.9	1824	42.5
Regional	221	48.0	279	42.0	356	41.1	443	39.7	443	37.3	1742	40.6
Distant	85	18.5	118	17.7	148	17.1	154	13.8	224	18.9	729	17.0
Missing	128	(21.8)	85	(11.3)	110	(11.3)	82	(6.8)	95	(7.4)	500	(10.4)
Stage (after imputation)												
Localized	191	32.5	294	39.2	406	41.6	556	46.4	559	43.6	2007	41.9
Regional	286	48.6	313	41.7	397	40.7	471	39.3	477	37.2	1944	40.5
Distant	111	18.9	143	19.1	173	17.7	171	14.3	246	19.2	845	17.6

Frequencies of stage before imputation are shown for the cases without missing stage information; on top of that is shown between parentheses the proportion of the missing stage.

For both colon and rectum cancer, the proportion of men and women cured from a local tumour rose steadily until the mid-1990s and reached a plateau over 85% (Tables 2 and 3; Supplementary Figs S5 and S6). The improvement over the study period was also impressive among the patients diagnosed with a regional tumour since the cure fraction more or less doubled and between 46 (men, rectum) and 57% (men, colon) of these patients were cured. Although the cure fraction also increased among the patients with a metastatic tumour, less than 7% of these patients were cured from 1996 to 2000. Apart from the last period of diagnosis, the MST for uncured lengthened considerably for all tumour stages, including the distant. This pattern was however somewhat attenuated for women with colon cancer.

The temporal patterns of the cure fraction and the MST for uncured patients were similar for the left and right colon. However, cure parameters were higher for the left colon (Table 2).

DISCUSSION

We observed a dramatic increase in cure fraction until the mid-1990s and a less noticeable lengthening of the MST for the uncured cases. All age groups and stage groups (with the exception of metastasis patients group) also showed a dramatic increase in cure fraction until the mid-1990s and then levelled-off. The overall increase in cure fraction might be due to both the shifting to a more favourable stage and the increase in age- and stage-specific cure fraction. Improvement in the management of colorectal cancer may also have played a role.

Distribution of age at diagnosis shifted considerably in the older groups from 1975 to 80 and 1996 to 2000: the under-50 age group, 22% of the patients in the first period represented less than 8% in the last period. However, trends in cure and MST for uncured were similar across all age groups. This explains why, after adjusting for other factors, age did not play a notable role in the observed improvements in cure parameters. At the same time, tumour stage at diagnosis shifted widely, mostly from regional to local stages and particularly until the mid-1990s. This shift is very likely to be related to the wider use of endoscopy to detect tumours at an earlier stage. While diagnostic endoscopy was used in less than 30% of colon cancer patients and less than 60% of rectal cancer patients in the late 1970s, the figures were around 80% in the late 1990s (13), an upper limit hard to exceed (Fig. 1). The more tumours were detected at earlier stage, the more curative resections were possible, as shown by the parallel trends in the proportion of curative resections (Fig. 1).

We have observed lower cure fraction in women, both overall and by age group, while stage-specific cure fractions were similar in both sexes. Women were diagnosed with more advanced stage than men (Table 1). We observed similar pattern for stomach cancer (14). Regular health monitoring is offered by large companies and for full-time workers, which means that women, more often part-time employees in small companies, may have fewer opportunities for earlier diagnosis than men.

These observations are good news and reflect a general improvement in the diagnosis and the treatment of these two cancers according to the interpretation of Verdecchia et al. (15). However, the figures showed some divergences from that general pattern. From the 1990, both cure fraction and MST for uncured levelled off or slightly decreased. This pattern was mostly seen among the patients at the localized tumour stage. It might reflect a change in patients' characteristics, in particular in the localized tumour group because of the wider use of early detection method, smaller tumours

Table 2. Trends in cure fraction (%) and median survival time for uncured patients (months), colon cancer, Osaka (Japan), 1975–2000

	Men		Women	
	Cure fraction (95% CI)	Median survival time (95% CI)	Cure fraction (95% CI)	Median survival time (95% CI)
All				
1975–1980	37.2 (33.2–41.3)	8.3 (7.1–9.7)	31.9 (28.0–36.0)	8.2 (7.0–9.5)
1981–1985	42.0 (38.8–45.2)	9.5 (8.5–10.7)	43.2 (40.1–46.4)	8.6 (7.7–9.5)
1986–1990	54.7 (52.1–57.3)	12.2 (11.0–13.7)	49.2 (46.6–51.8)	11.7 (10.7–12.7)
1991–1995	67.0 (65.0–69.0)	10.8 (9.8–12.0)	57.6 (55.4–59.7)	10.6 (9.7–11.6)
1996–2000	62.0 (60.1–64.0)	11.7 (10.7–12.7)	57.5 (55.5–59.5)	10.6 (9.8–11.5)
By age				
<50				
1975–1980	41.4 (36.7–46.2)	10.4 (8.6–12.6)	34.6 (29.9–39.6)	10.6 (8.9–12.6)
1981–1985	47.0 (42.9–51.2)	12.5 (10.7–14.6)	47.0 (42.9–51.2)	10.6 (9.4–12.1)
1986–1990	58.9 (55.1–62.5)	16.0 (13.8–18.7)	52.9 (49.1–56.7)	14.6 (13.0–16.4)
1991–1995	70.9 (67.8–73.8)	13.7 (11.7–15.9)	61.5 (58.0–64.8)	13.9 (12.3–15.7)
1996–2000	66.9 (63.6–70.1)	15.0 (13.0–17.2)	62.4 (58.9–65.8)	13.9 (12.4–15.6)
50–59				
1975–1980	39.6 (35.1–44.2)	10.7 (9.0–12.8)	34.4 (29.9–39.2)	10.9 (9.3–12.9)
1981–1985	45.2 (41.5–48.9)	12.7 (11.1–14.4)	46.9 (43.1–50.7)	11.0 (9.7–12.3)
1986–1990	57.0 (53.9–60.1)	16.0 (14.1–18.2)	52.8 (49.4–56.1)	15.1 (13.6–16.7)
1991–1995	69.3 (66.8–71.7)	13.8 (12.3–15.4)	61.3 (58.4–64.2)	14.4 (12.9–16.1)
1996–2000	65.2 (62.6–67.8)	15.0 (13.5–16.6)	62.3 (59.4–65.1)	14.4 (13.0–15.9)
60–69				
1975–1980	38.0 (33.6–42.6)	8.7 (7.3–10.5)	35.1 (30.7–39.8)	8.8 (7.4–10.3)
1981–1985	43.5 (39.8–47.3)	10.6 (9.2–12.2)	47.6 (43.9–51.4)	9.1 (8.0–10.3)
1986–1990	55.4 (52.1–58.6)	13.7 (12.0–15.6)	53.5 (50.3–56.8)	12.8 (11.4–14.3)
1991–1995	67.9 (65.3–70.4)	11.7 (10.3–13.3)	62.1 (59.3–64.7)	12.0 (10.7–13.4)
1996–2000	63.7 (61.2–66.1)	12.9 (11.7–14.3)	63.0 (60.4–65.6)	12.2 (11.1–13.5)
70–79				
1975–1980	35.1 (30.7–39.8)	5.1 (4.2–6.2)	28.5 (24.5–32.9)	6.6 (5.5–7.9)
1981–1985	40.5 (36.6–44.5)	6.5 (5.5–7.6)	40.1 (36.5–43.9)	7.1 (6.3–8.1)
1986–1990	52.3 (48.6–55.9)	8.5 (7.3–9.8)	45.9 (42.6–49.3)	10.2 (9.1–11.5)
1991–1995	65.1 (62.0–68.1)	7.3 (6.4–8.5)	54.6 (51.5–57.8)	9.4 (8.3–10.6)
1996–2000	60.8 (57.7–63.7)	8.3 (7.4–9.4)	55.6 (52.7–58.6)	9.8 (8.8–10.8)
80+				
1975–1980	29.2 (23.8–35.1)	2.2 (1.7–2.9)	18.6 (15.2–22.6)	3.2 (2.6–4.0)
1981–1985	34.1 (28.8–39.9)	3.0 (2.4–3.8)	27.7 (23.9–31.9)	3.9 (3.3–4.6)
1986–1990	45.5 (39.8–51.2)	4.0 (3.1–5.0)	32.7 (28.8–36.9)	5.6 (4.9–6.5)
1991–1995	58.7 (53.3–63.9)	3.5 (2.8–4.4)	40.8 (36.7–45.1)	4.9 (4.3–5.7)
1996–2000	54.1 (48.7–59.4)	4.2 (3.4–5.2)	41.8 (37.9–45.9)	5.4 (4.8–6.2)

Continued

Table 2. *Continued*

	Men		Women	
	Cure fraction (95% CI)	Median survival time (95% CI)	Cure fraction (95% CI)	Median survival time (95% CI)
By stage				
Localized				
1975–1980	71.2 (65.0–81.6)	25.2 (6.8–93.3)	71.8 (65.2–77.6)	22.0 (16.1–30.0)
1981–1985	80.2 (72.4–86.2)	35.2 (16.9–73.4)	84.1 (80.6–87.0)	19.3 (15.3–24.3)
1986–1990	85.1 (78.9–89.8)	45.0 (21.2–95.7)	86.5 (83.8–88.8)	24.0 (19.6–29.4)
1991–1995	89.1 (84.2–92.7)	47.9 (21.9–104.7)	89.1 (87.0–90.9)	25.4 (20.2–32.1)
1996–2000	89.7 (85.1–93.0)	43.1 (21.1–88.0)	89.8 (87.8–91.6)	24.0 (19.3–29.9)
Regional				
1975–1980	30.2 (25.2–35.8)	11.3 (9.6–13.4)	25.0 (20.1–30.6)	11.4 (9.5–13.6)
1981–1985	37.9 (33.6–42.5)	13.6 (12.0–15.4)	40.8 (36.6–45.2)	11.3 (10.1–12.6)
1986–1990	46.3 (42.1–50.6)	16.7 (14.9–18.7)	45.6 (41.7–49.5)	14.7 (13.4–16.2)
1991–1995	55.3 (51.4–59.2)	17.5 (15.6–19.6)	51.7 (48.2–55.3)	14.7 (13.2–16.2)
1996–2000	56.9 (53.2–60.4)	16.9 (15.3–18.7)	53.7 (50.3–57.0)	14.3 (13.1–15.7)
Distant				
1975–1980	2.4 (1.7–3.3)	5.2 (4.5–6.1)	1.4 (0.9–2.0)	5.2 (4.5–6.2)
1981–1985	3.3 (2.6–4.3)	6.5 (5.8–7.3)	2.8 (2.1–3.7)	6.0 (5.4–6.7)
1986–1990	4.7 (3.6–5.9)	8.1 (7.3–8.9)	3.4 (2.5–4.4)	8.1 (7.5–8.9)
1991–1995	6.5 (5.3–8.1)	8.4 (7.7–9.2)	4.3 (3.3–5.5)	7.5 (6.9–8.2)
1996–2000	6.9 (5.6–8.5)	8.6 (7.9–9.3)	4.6 (3.6–5.9)	7.7 (7.1–8.3)
By subsite				
Right				
1975–1980	33.1 (29.2–37.3)	7.4 (6.3–8.8)	27.8 (24.0–31.8)	7.5 (6.4–8.8)
1981–1985	37.1 (33.7–40.7)	8.6 (7.5–9.9)	38.0 (34.7–41.4)	7.9 (7.1–8.9)
1986–1990	49.3 (46.0–52.6)	11.1 (9.8–12.6)	43.9 (41.0–46.9)	10.8 (9.8–11.9)
1991–1995	61.9 (59.1–64.6)	10.0 (8.9–11.2)	52.3 (49.7–54.9)	9.9 (8.9–10.9)
1996–2000	57.1 (54.4–59.8)	10.8 (9.7–11.9)	52.8 (50.4–55.3)	9.9 (9.0–10.8)
Left				
1975–1980	41.0 (36.7–45.5)	8.9 (7.5–10.6)	35.6 (31.3–40.1)	8.9 (7.6–10.5)
1981–1985	45.3 (41.9–48.9)	10.2 (9.0–11.6)	46.8 (43.5–50.2)	9.2 (8.2–10.3)
1986–1990	57.7 (54.8–60.5)	13.1 (11.6–14.8)	53.0 (50.1–55.8)	12.5 (11.3–13.9)
1991–1995	69.5 (67.3–71.7)	11.8 (10.5–13.2)	61.2 (58.8–63.5)	11.6 (10.4–12.9)
1996–2000	65.2 (62.9–67.4)	12.5 (11.4–13.8)	61.7 (59.3–64.0)	11.4 (10.4–12.6)

CI, confidence interval.

were found and were curatively resected. However, more *in situ* tumours were diagnosed and removed from the localized tumour group, leaving the 'more advanced' cases within the localized tumour group. Although only 20% of the target population in Osaka is covered by the mass-screening programme (16), such a stage-shifting phenomenon is quite similar to what has been observed in cervical cancer in countries with high screening coverage, in which survival plateaued or even declined (17). It may reflect the high use of opportunistic screening.

The cure fraction of colorectal cancer in Osaka was generally higher than in other countries. For example, in the EUROCARE study, the cure fraction ranged between 24.8 and 48.0% for patients diagnosed from 1988 to 99 (18). This could be largely attributable to the differences in stage distribution. In Osaka, the advanced stage (distant metastasis) constituted 23% of colon cancer and 18.6% of rectal cancer from 1996 to 2000, whereas in Europe, the proportion of advanced stage for colorectal cancer ranged between 25% (France) and 37% (Poland) between 1996 and 1998 (19).

Table 3. Trends in cure fraction (%) and median survival time for uncured patients (months), rectal cancer, Osaka (Japan), 1975–2000

	Men		Women	
	Cure fraction (95% CI)	Median survival time (months) (95% CI)	Cure fraction (95% CI)	Median survival time (months) (95% CI)
All				
1975–1980	31.3 (27.4–35.6)	14.5 (12.7–16.5)	24.9 (20.3–30.2)	15.0 (12.6–17.8)
1981–1985	40.9 (37.4–44.5)	15.8 (14.0–17.7)	41.9 (37.9–46.1)	15.6 (13.7–17.7)
1986–1990	51.1 (48.1–54.1)	18.4 (16.8–20.2)	48.0 (44.3–51.8)	19.4 (17.2–22.0)
1991–1995	54.9 (52.0–57.8)	20.5 (18.4–22.8)	58.3 (55.0–61.6)	19.7 (17.6–22.2)
1996–2000	57.0 (54.5–59.4)	17.5 (16.2–18.9)	56.5 (53.3–59.7)	16.5 (14.8–18.3)
By age				
<50				
1975–1980	31.3 (26.8–36.2)	18.6 (16.0–21.5)	25.4 (20.4–31.1)	19.8 (16.6–23.6)
1981–1985	41.7 (37.5–46.0)	19.4 (17.1–21.9)	42.6 (37.6–47.7)	19.4 (16.9–22.2)
1986–1990	50.9 (46.9–54.9)	21.7 (19.5–24.2)	48.0 (43.4–52.7)	24.1 (21.1–27.5)
1991–1995	54.7 (50.7–58.7)	24.5 (21.6–27.7)	58.0 (53.5–62.4)	23.9 (21.2–26.9)
1996–2000	56.8 (52.9–60.7)	20.9 (18.9–23.2)	56.8 (52.1–61.4)	20.7 (18.4–23.2)
50–59				
1975–1980	34.9 (30.2–40.0)	18.5 (15.7–21.6)	28.2 (22.7–34.3)	17.4 (14.1–21.3)
1981–1985	45.7 (41.5–49.9)	19.3 (16.9–22.1)	46.0 (41.0–51.2)	17.5 (15.1–20.3)
1986–1990	55.0 (51.3–58.5)	21.9 (19.7–24.3)	51.6 (46.9–56.2)	22.1 (19.0–25.7)
1991–1995	58.7 (55.2–62.1)	24.8 (21.8–28.1)	61.4 (57.2–65.5)	22.1 (19.3–25.4)
1996–2000	60.8 (57.5–63.9)	21.1 (19.1–23.2)	60.2 (56.0–64.3)	19.1 (17.0–21.5)
60–69				
1975–1980	32.3 (27.9–37.2)	13.6 (11.7–15.9)	28.5 (23.2–34.6)	16.2 (13.3–19.6)
1981–1985	42.8 (38.7–47.1)	14.6 (12.7–16.7)	46.5 (41.5–51.6)	16.5 (14.2–19.2)
1986–1990	52.1 (48.4–55.8)	17.2 (15.4–19.2)	52.0 (47.2–56.8)	20.8 (17.9–24.3)
1991–1995	55.9 (52.4–59.3)	18.9 (16.8–21.3)	61.9 (57.6–65.9)	21.0 (18.3–24.0)
1996–2000	58.0 (54.9–61.0)	16.7 (15.3–18.3)	60.7 (56.6–64.6)	18.2 (16.2–20.4)
70–79				
1975–1980	28.8 (24.1–33.9)	11.0 (9.1–13.3)	23.2 (18.3–29.0)	10.5 (8.2–13.4)
1981–1985	38.8 (34.1–43.6)	12.1 (10.1–14.3)	39.7 (34.3–45.5)	11.8 (9.6–14.4)
1986–1990	47.9 (43.3–52.5)	15.0 (12.9–17.4)	45.1 (39.7–50.6)	15.3 (12.6–18.7)
1991–1995	51.7 (47.0–56.4)	16.3 (13.7–19.3)	55.2 (50.0–60.2)	16.0 (13.3–19.3)
1996–2000	53.8 (49.5–58.1)	14.6 (12.8–16.7)	53.9 (48.9–58.8)	13.9 (11.8–16.3)
80+				
1975–1980	21.2 (15.7–27.8)	4.9 (3.5–6.7)	15.8 (11.1–21.8)	4.7 (3.3–6.7)
1981–1985	29.6 (23.1–37.0)	5.7 (4.3–7.6)	28.9 (22.2–36.7)	6.1 (4.5–8.2)
1986–1990	37.9 (30.6–45.9)	7.9 (6.2–10.2)	33.7 (26.4–41.8)	7.9 (5.8–10.7)
1991–1995	41.6 (34.1–49.5)	8.0 (6.0–10.5)	43.2 (35.3–51.4)	8.8 (6.6–11.6)
1996–2000	43.7 (36.1–51.5)	8.0 (6.3–10.1)	41.9 (34.4–49.9)	7.9 (6.2–10.0)

Continued

Table 3. *Continued*

	Men		Women	
	Cure fraction (95% CI)	Median survival time (months) (95% CI)	Cure fraction (95% CI)	Median survival time (months) (95% CI)
By stage				
Localized				
1975–1980	65.4 (61.0–73.7)	26.8 (10.8–66.6)	53.2 (42.7–63.5)	34.9 (24.2–50.3)
1981–1985	75.6 (70.6–80.0)	32.0 (25.9–39.5)	72.2 (64.4–78.9)	38.2 (26.6–54.8)
1986–1990	81.8 (78.3–84.9)	33.3 (27.7–40.0)	78.3 (72.0–83.5)	43.2 (30.6–61.1)
1991–1995	83.1 (79.8–86.0)	39.1 (31.6–48.4)	84.4 (79.5–88.3)	42.6 (30.1–60.3)
1996–2000	85.9 (83.1–88.3)	31.8 (26.5–38.0)	85.5 (80.5–89.3)	38.4 (27.5–53.6)
Regional				
1975–1980	23.0 (18.7–27.9)	18.7 (16.6–21.2)	15.3 (11.2–20.6)	16.7 (14.5–19.4)
1981–1985	30.6 (26.5–35.0)	20.3 (18.3–22.5)	29.2 (24.5–34.4)	19.8 (17.6–22.2)
1986–1990	39.0 (35.0–43.1)	22.4 (20.6–24.4)	36.4 (31.7–41.3)	22.4 (20.1–25.0)
1991–1995	41.2 (37.2–45.3)	25.0 (22.8–27.5)	46.2 (41.6–50.8)	22.7 (20.5–25.2)
1996–2000	46.4 (42.8–50.1)	21.8 (20.3–23.5)	48.3 (43.5–53.0)	21.3 (19.3–23.4)
Distant				
1975–1980	2.4 (1.7–3.4)	7.3 (6.2–8.6)	1.0 (0.6–1.7)	6.0 (4.9–7.4)
1981–1985	3.5 (2.5–4.7)	8.5 (7.4–9.8)	2.3 (1.5–3.6)	8.5 (7.3–10.0)
1986–1990	5.0 (3.7–6.7)	11.0 (9.9–12.2)	3.2 (2.1–4.9)	10.1 (8.7–11.7)
1991–1995	5.4 (4.1–7.2)	11.3 (10.0–12.7)	4.7 (3.1–7.0)	10.8 (9.3–12.4)
1996–2000	6.6 (5.1–8.6)	11.1 (10.1–12.1)	5.1 (3.4–7.6)	10.4 (9.3–11.8)

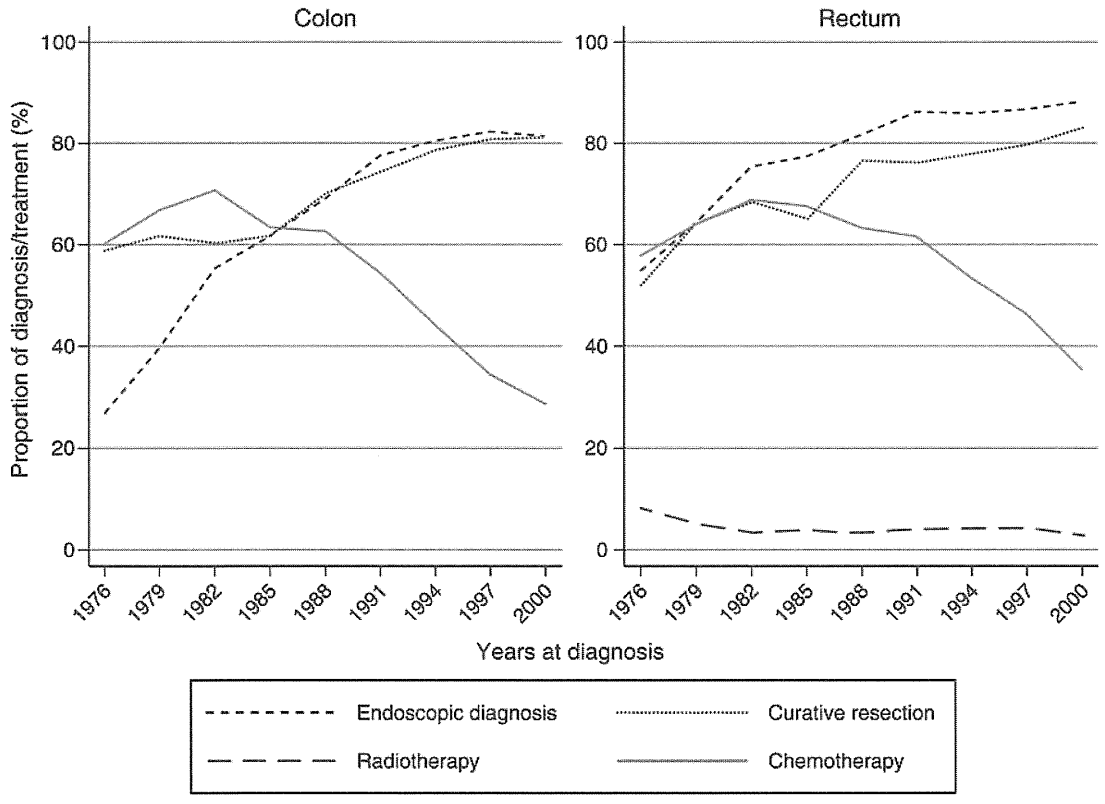

Figure 1. Trends in the diagnostic method and treatment for colorectal cancer in Osaka, Japan, in 1975–2001.

This may be related to the difference in the use of endoscopic diagnosis in clinical settings between countries. Increasing in cure fraction and MST for uncured patients was also observed in Finland for colorectal cancer. While in the early 1970s, both cure parameters were comparable for all age groups in Finland and Osaka, the bigger increase in cure fraction observed in Osaka in the late 1990s was obtained to the cost of shorter MST for uncured patients, in comparison with Finland, regardless the age group (20). It is striking that this shortening in MST occurred while the use of in particular chemotherapy dramatically decreased (Fig. 1).

Compared with analysis on data after imputation, the complete-case analysis showed slightly higher cure fractions and longer MST for uncured cases, especially among localized stage patients. Such over-estimations hardly modify the interpretation of our findings.

This study was implemented using population-based cancer registry data in Osaka. Compared with hospital series and hospital-based cancer registry data, the information available in our study was limited, which prevented us from evaluating the influence of type of treatment and detection method on the trends in cure parameters. However, in contrast to the clinical database, our study included all cancer cases within defined geographical areas, regardless of their age, co-morbidities or prognosis. Furthermore, our population-based results, among the highest cure fraction worldwide, show that since virtually all colorectal cancer patients are diagnosed by endoscopy and received surgical treatment with curative intent, any further progress in survival and cure is likely to require new, innovative strategies of colorectal cancer management.

Supplementary data

Supplementary data are available at http://www.jjco.oxfordjournals.org.

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Conflict of interest statement

None declared.

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第3章

がんの罹患と死亡動向の府県別分析

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