Operation (2016/01/04)

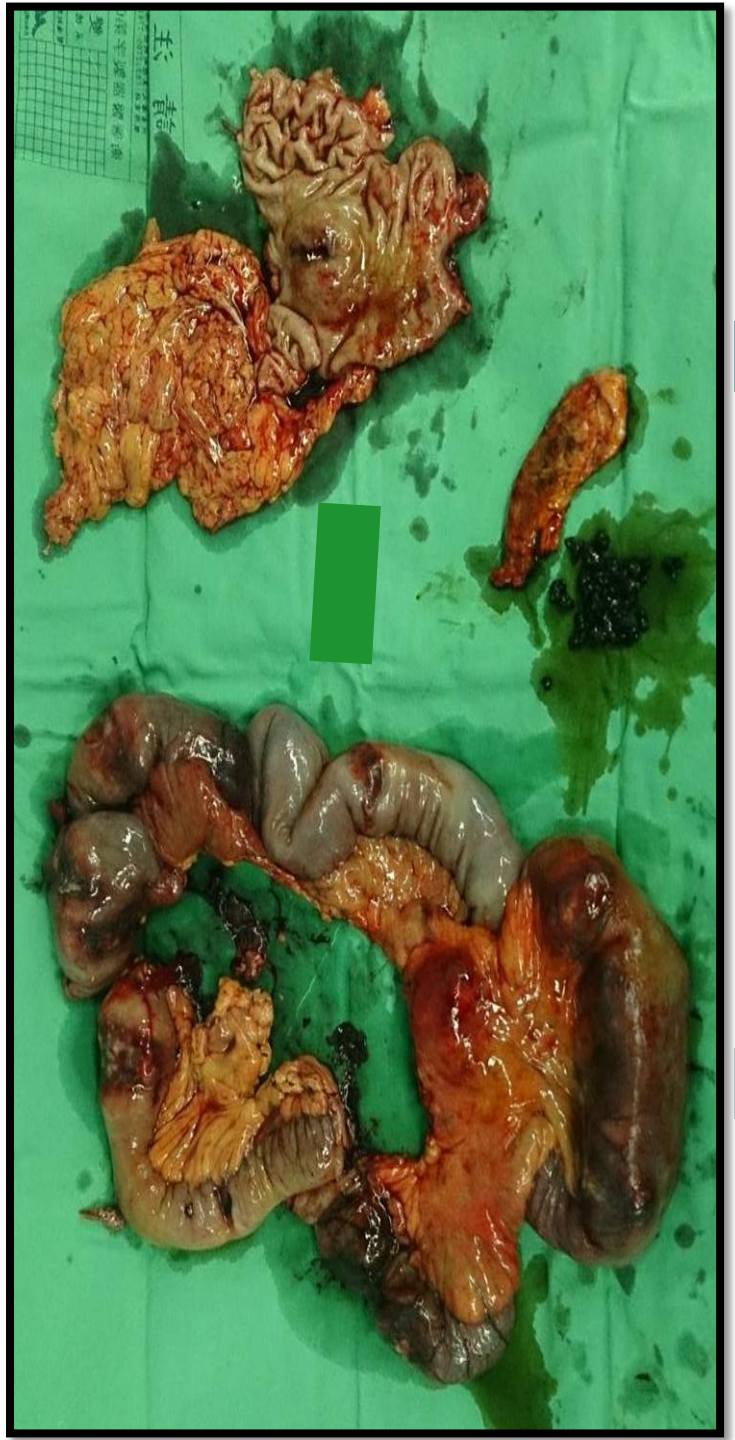
- Operative findings
  - A 3cm ulcerative tumor in the lesser curvature side of distal stomach at angularis.
  - Multiple tumor masses in the jejunum from proximal jejunum (10cm distal to Treitz's ligament) to distal jejunum
  - Lymph nodes enlargement over the 4^{th} portion of duodenum
  - Multiple gall stones in the gall bladder

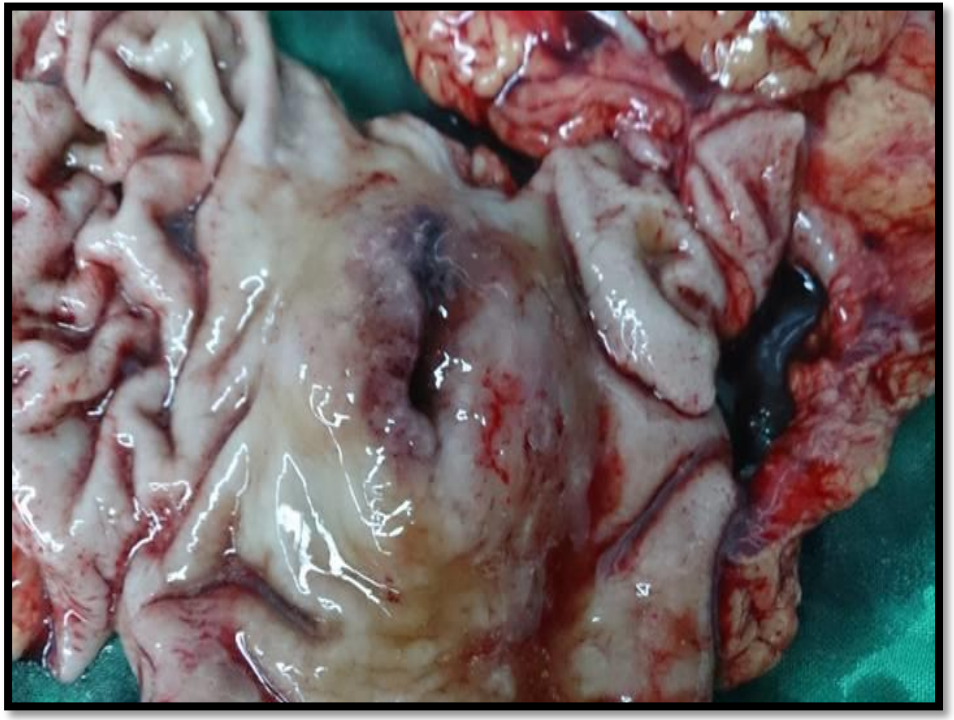
- Operation procedures
  - Hemigastrectomy with gastrojejunostomy
  - Segmental resection of jejunum with end-to-end anastamosis
  - Cholecystectomy

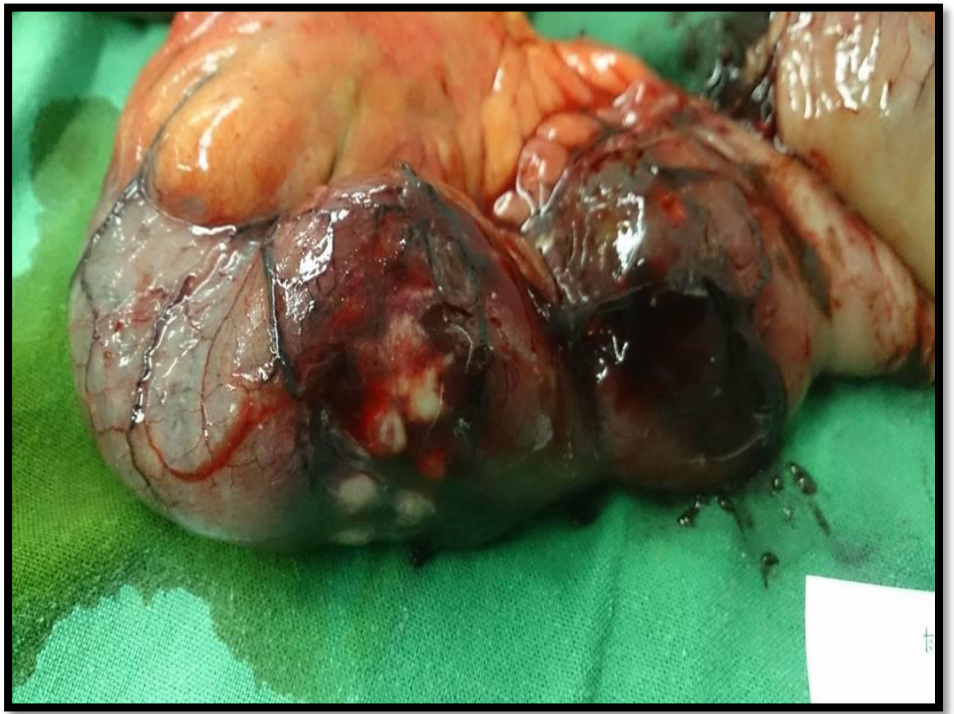
病理科

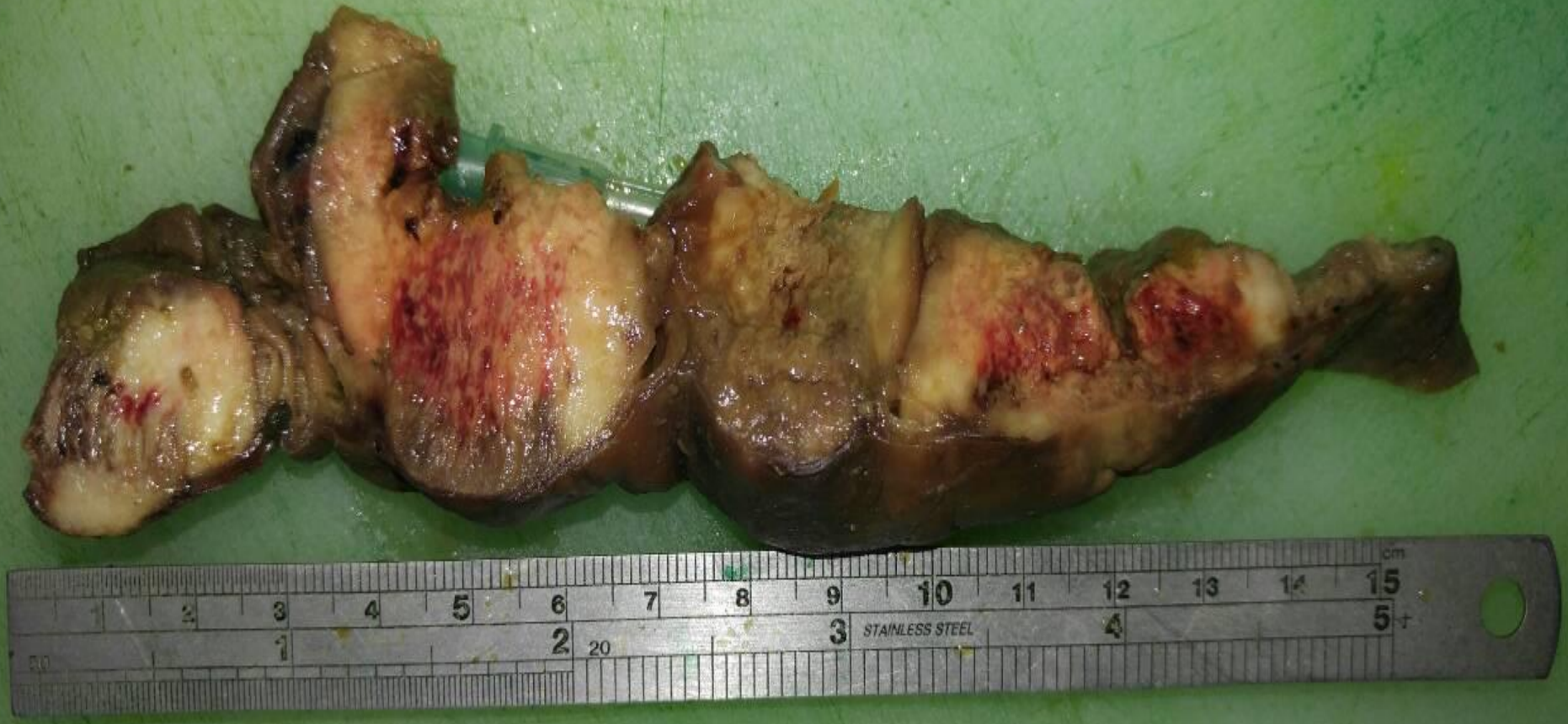
105-6-25

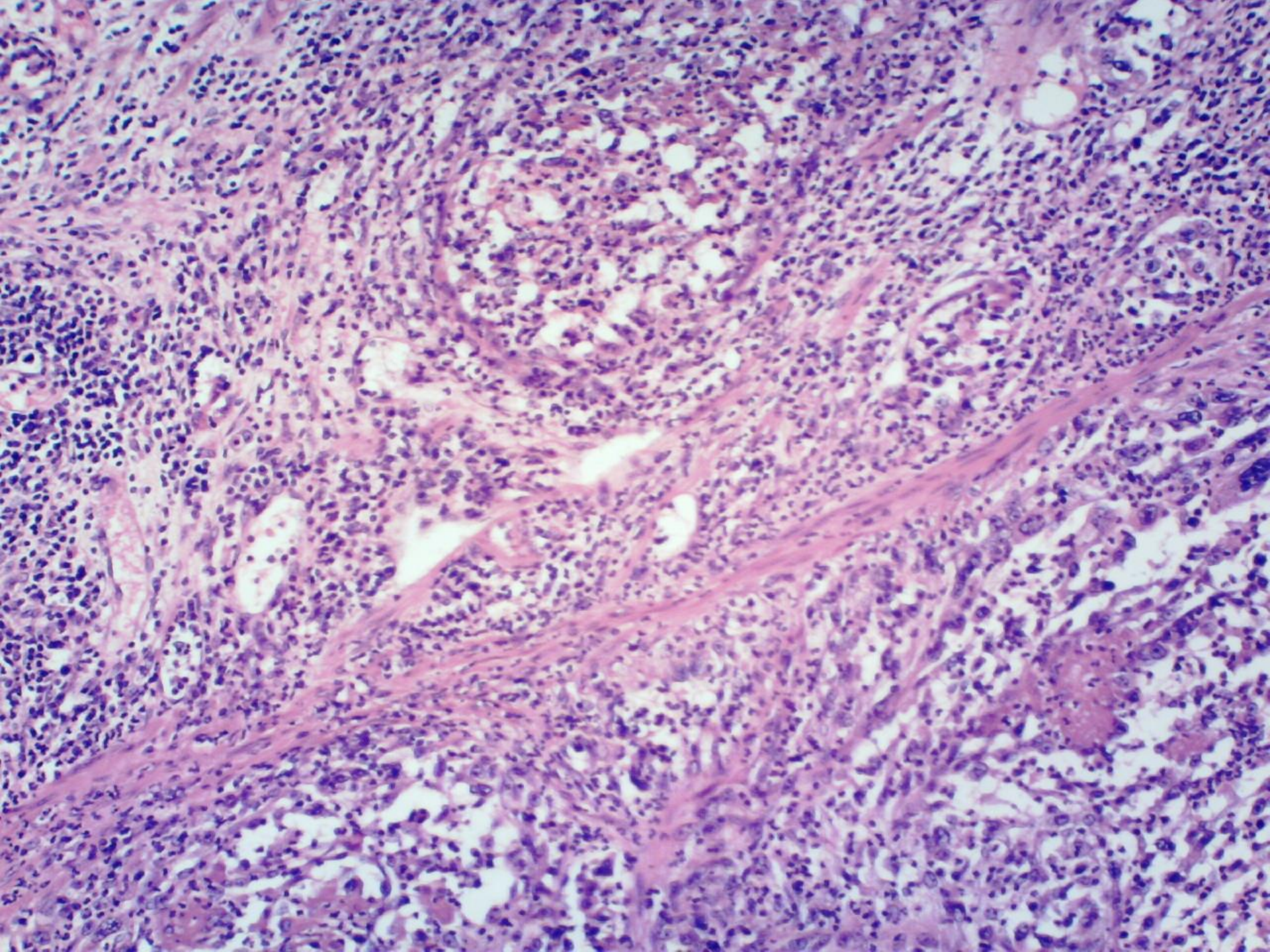
周醫師

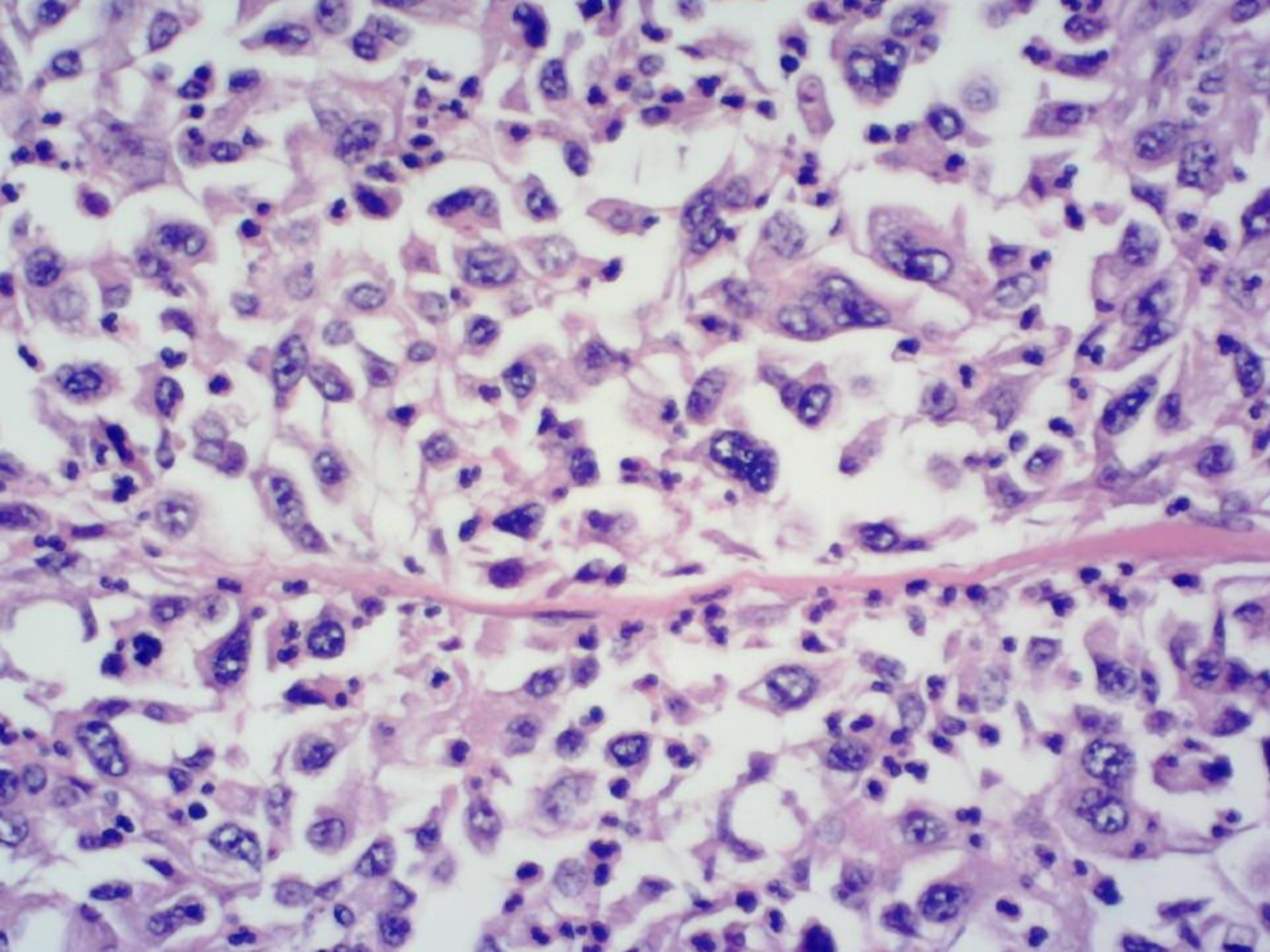


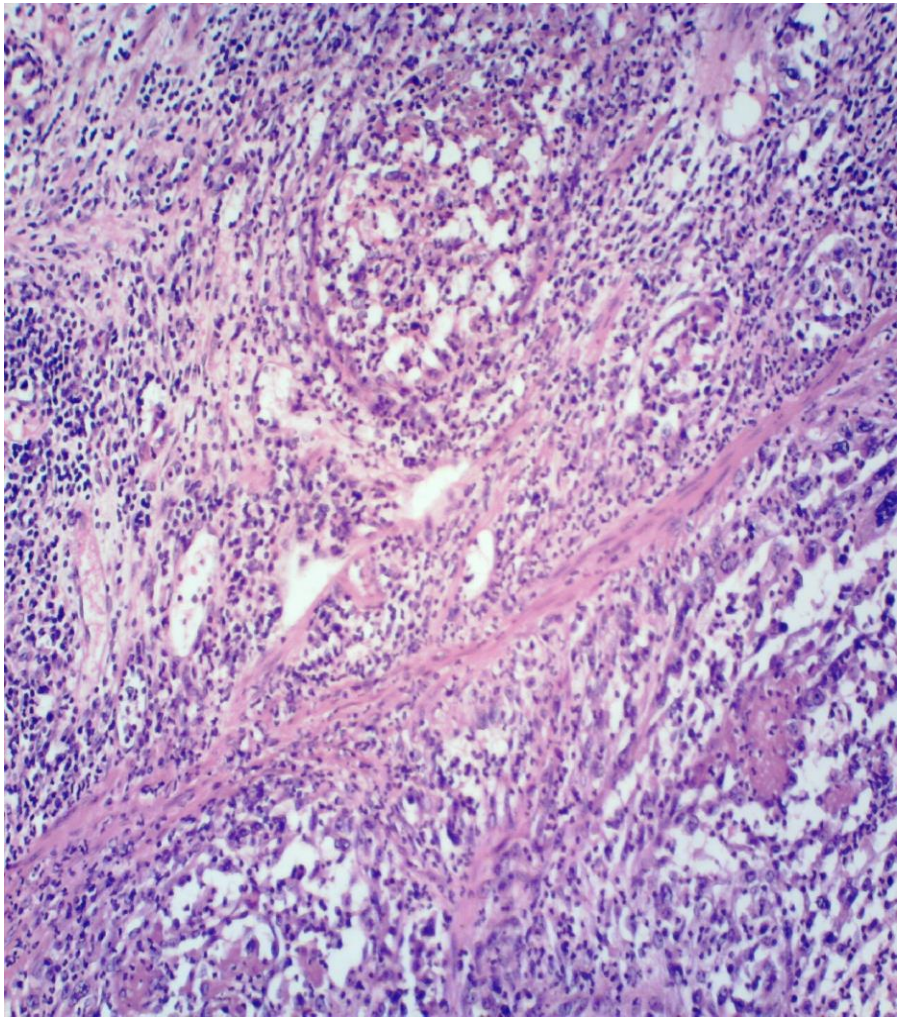


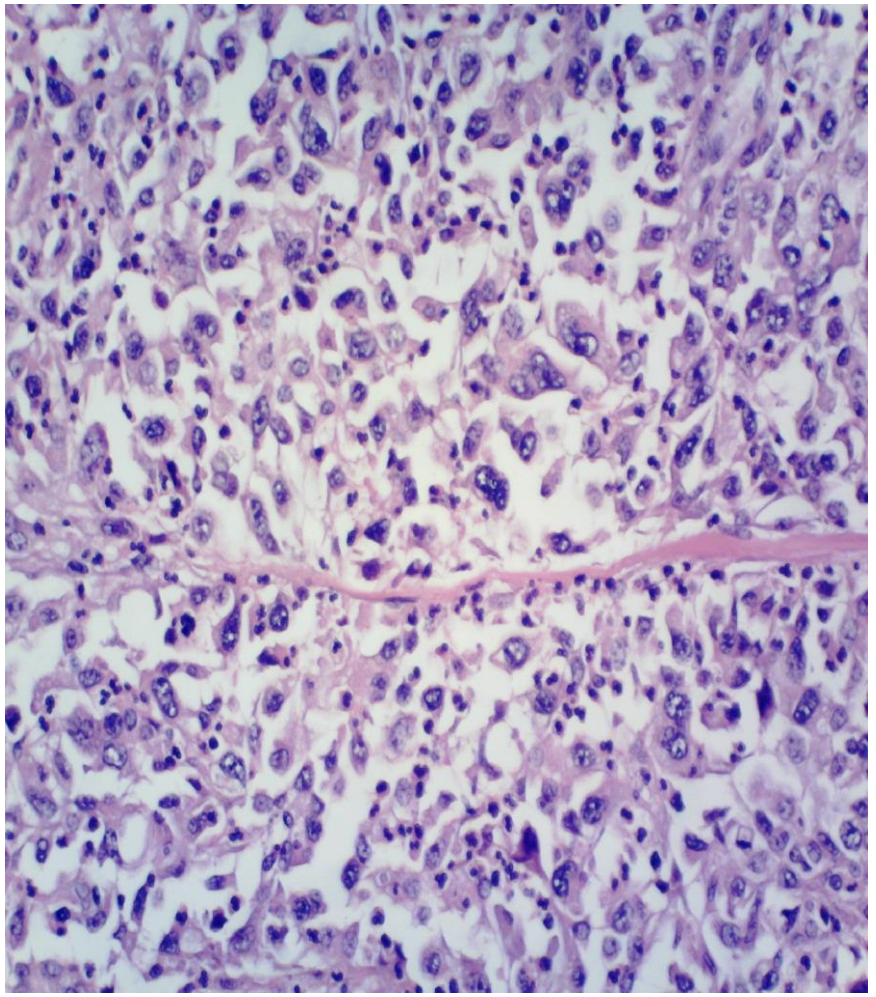


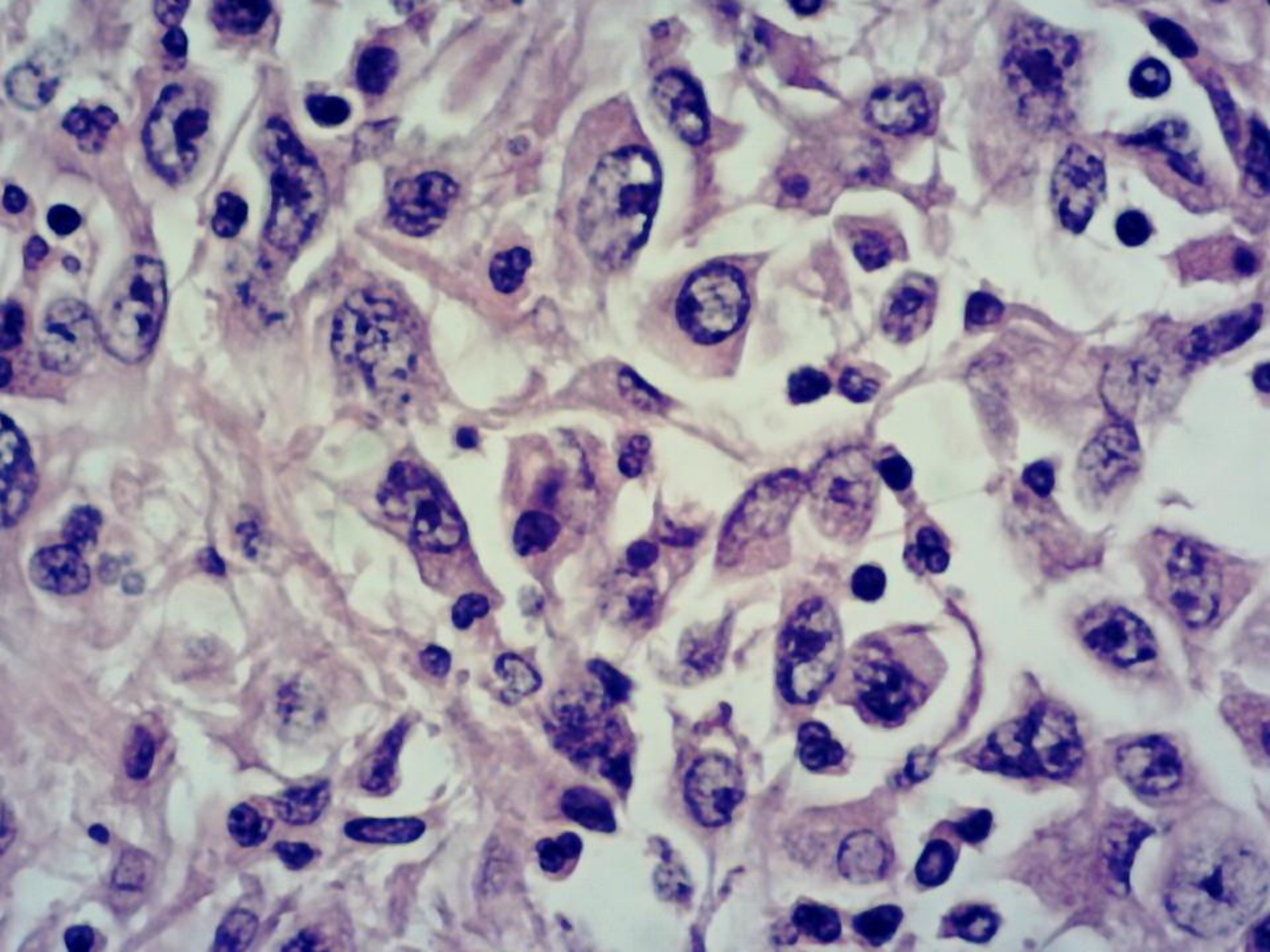

STAINLESS STEEL

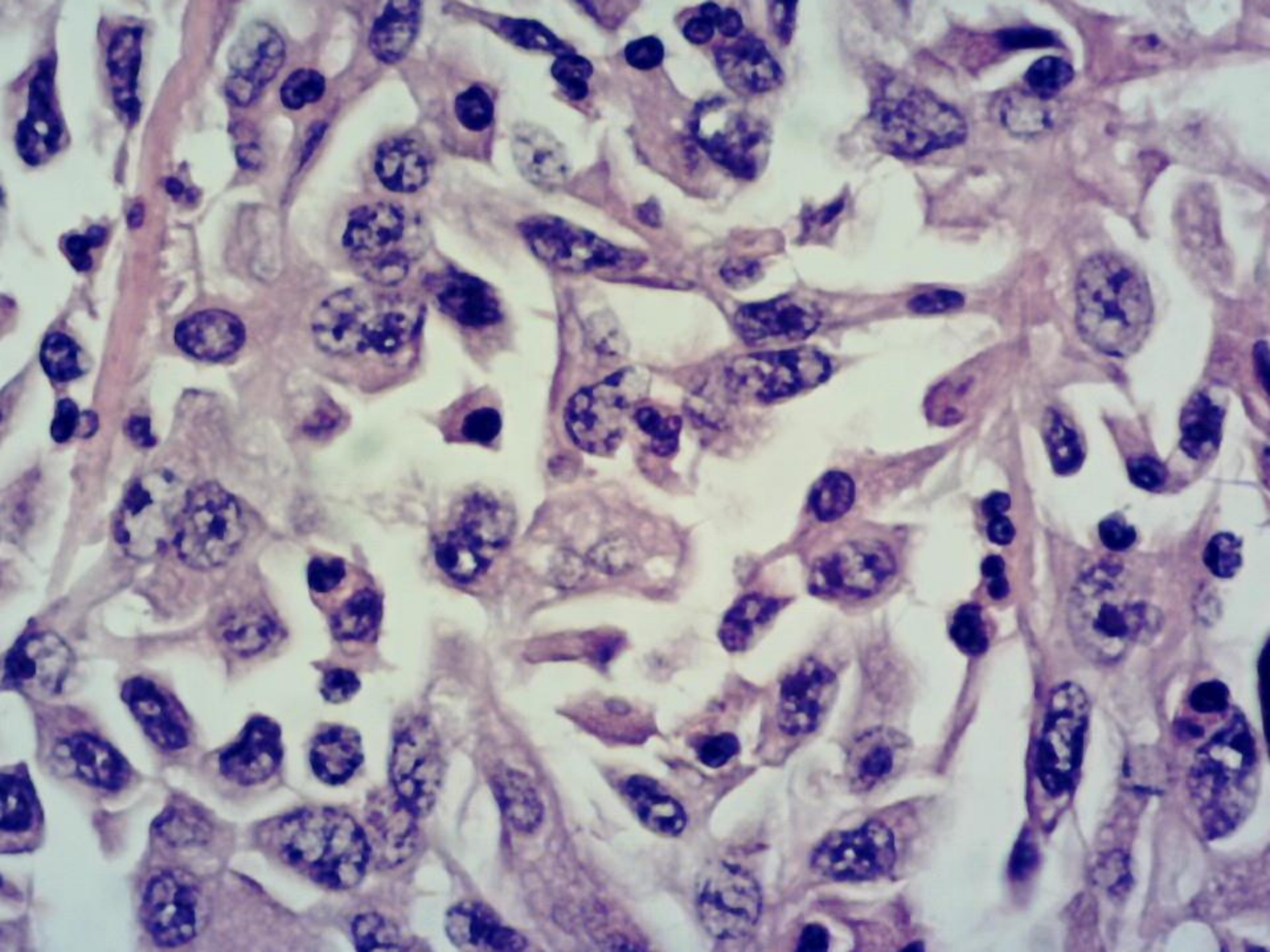


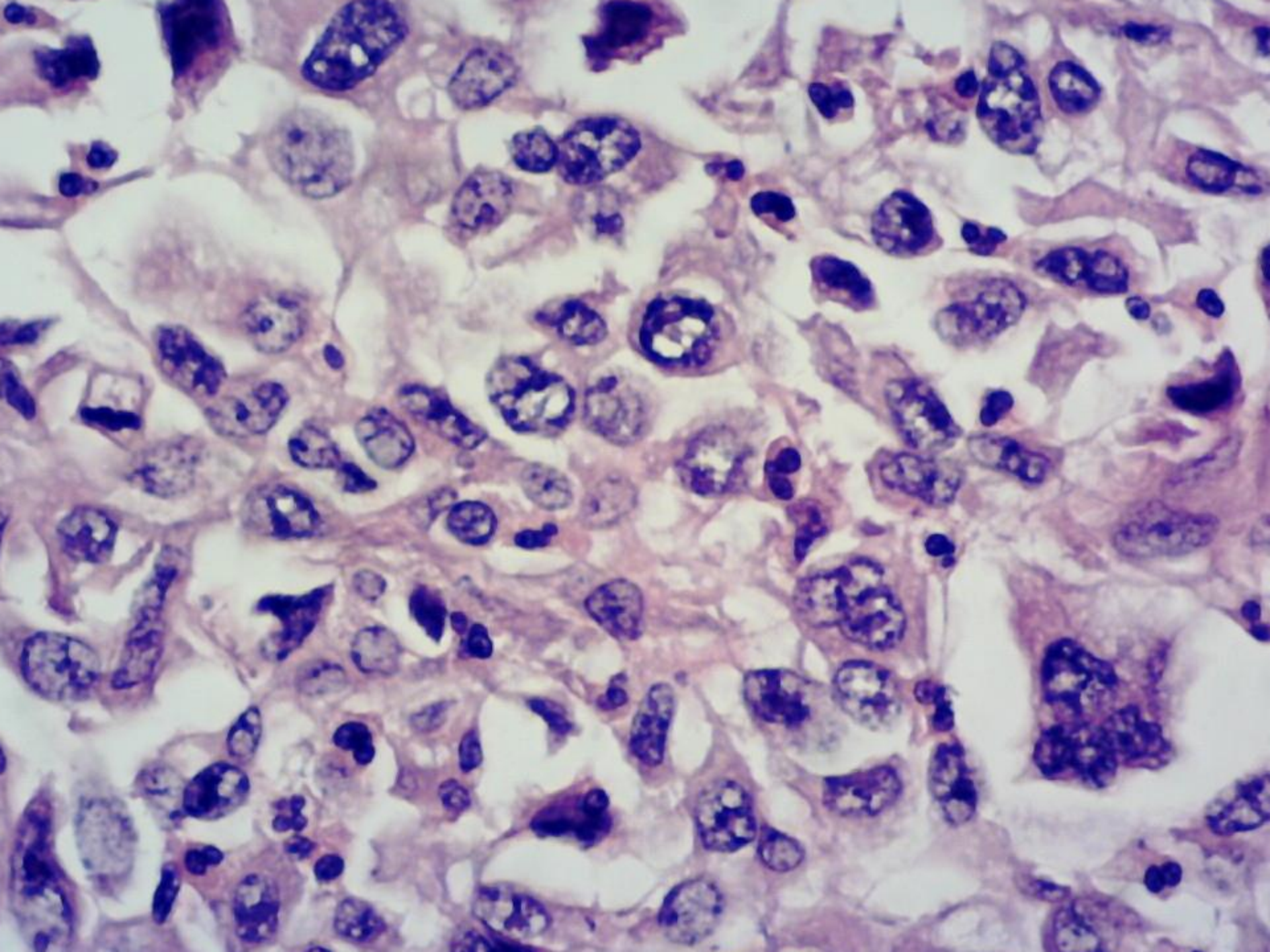


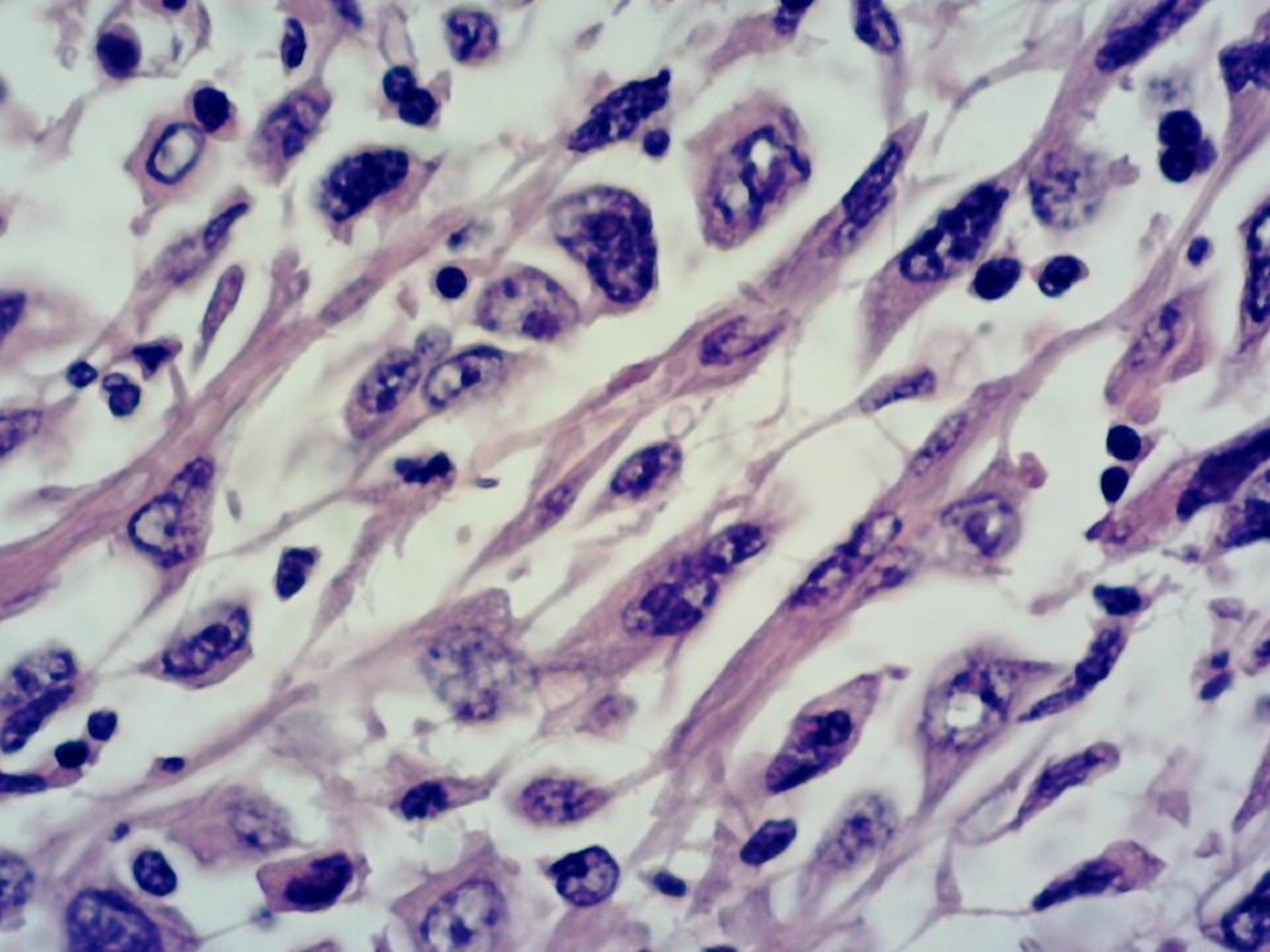


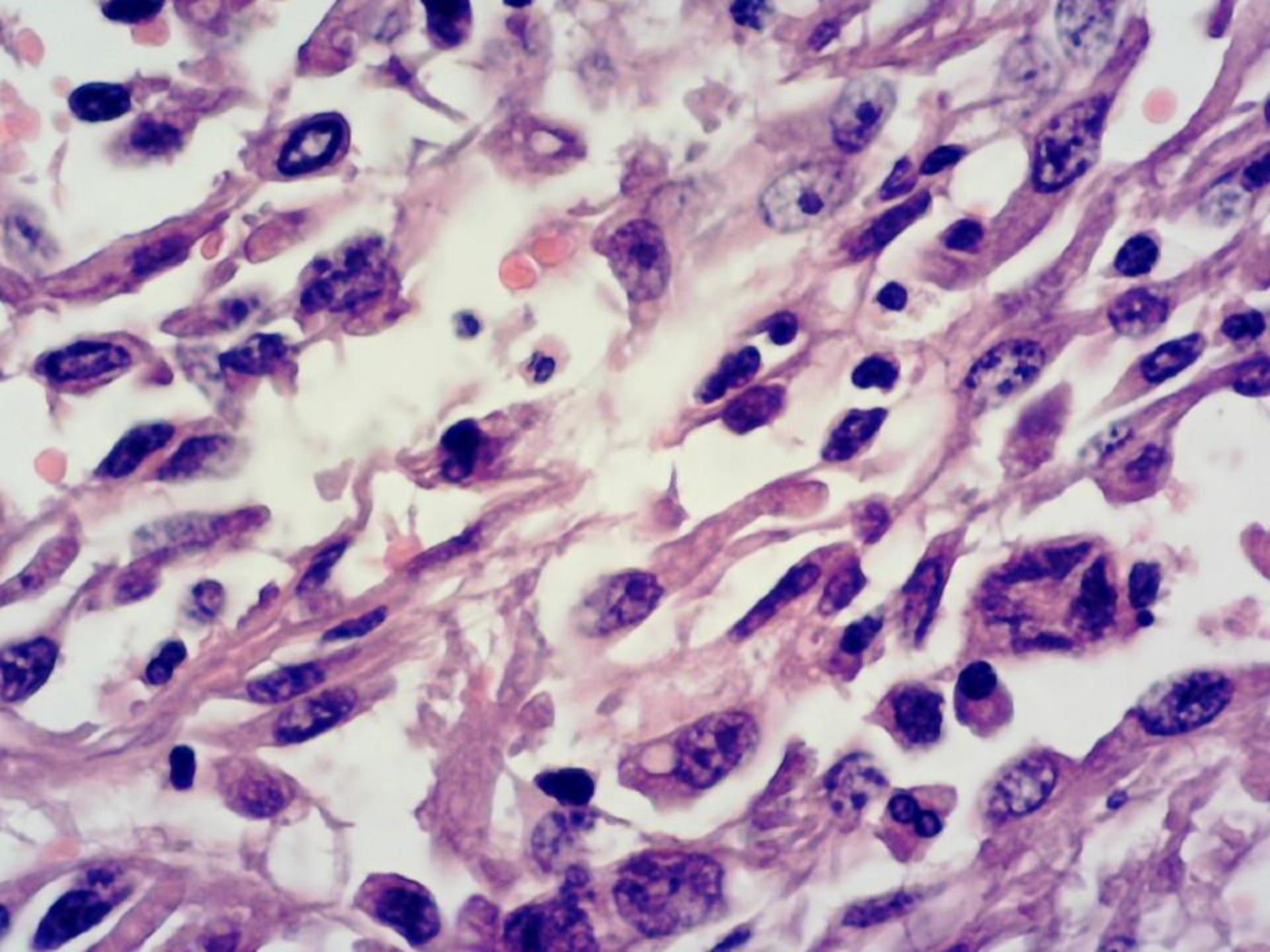


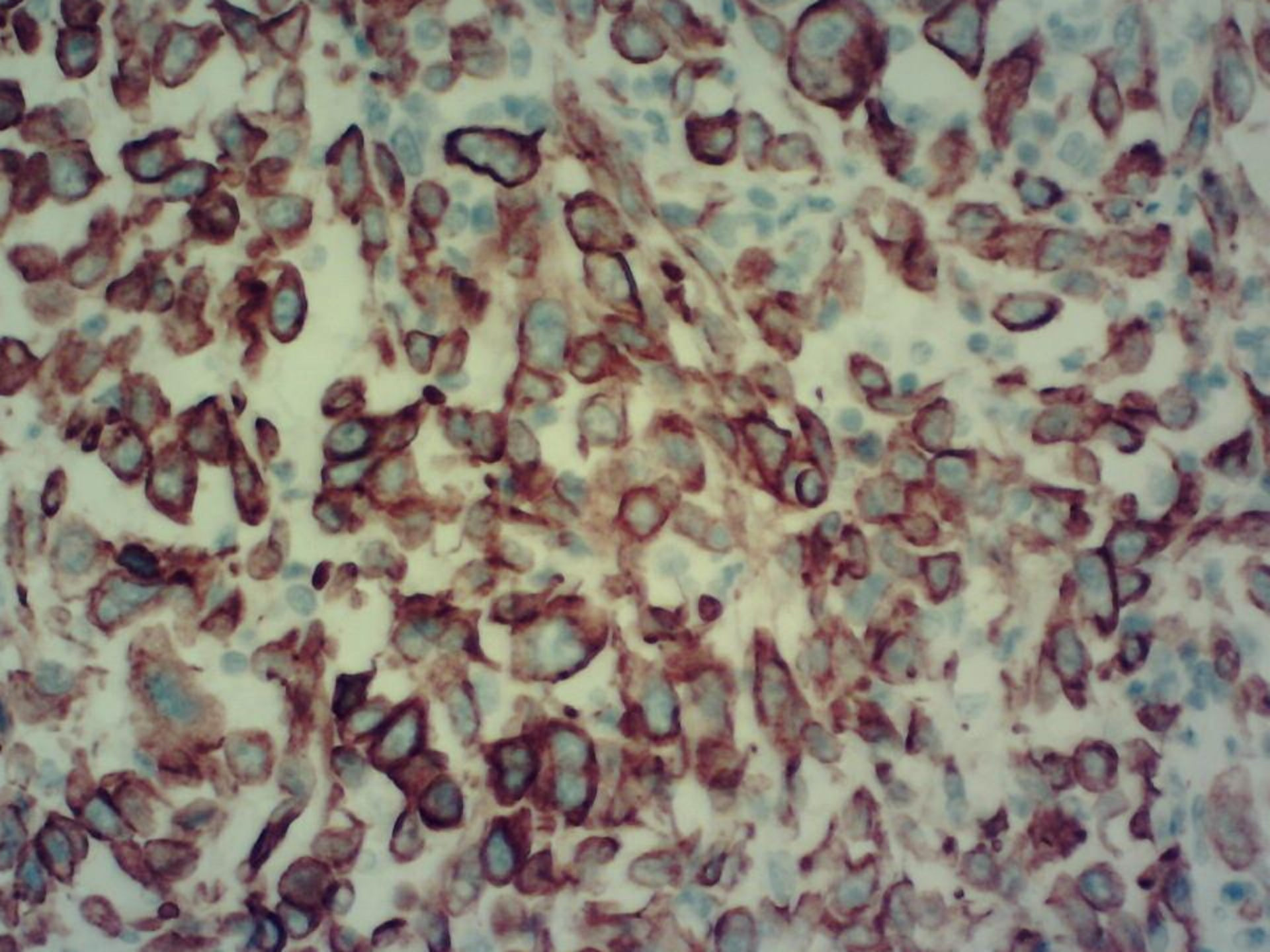


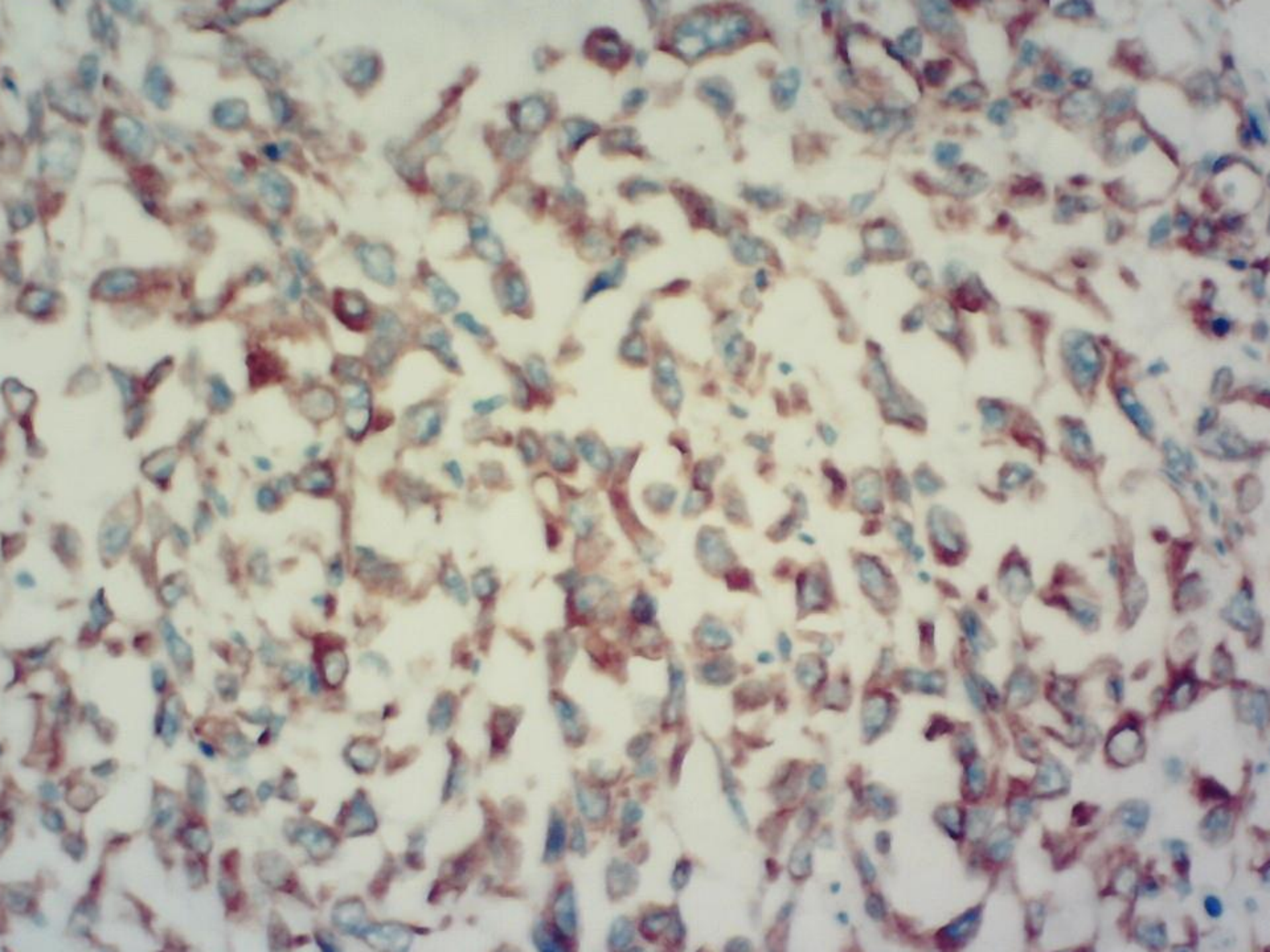












Immunohistochemistry

CK(+)
P63(-)
CD117(-)
SMA(-)
EMA(-)
CD21(-)
CK7(-)
WT-1(-)

Vimentin(+)
S100(-)
CD34(-)
CD30(-)
Bcl2(-)
CD1a(-)
CK20(-)
Calretinin(-)

PATHOLOGICAL DIAGNOSIS

Intestine, jejunum, resection, sarcomatoid carcinoma.

Stomach, hemigastrectomy, sarcomatoid carcinoma, metastatic.

A604524/105-00079

Sarcomatoid carcinoma of the small intestine: a case report and review of the literature.

Abstract

Sarcomatoid carcinoma of the small bowel is rare; to our knowledge, 19 cases have been reported to date in the English literature under several names. We report an additional case occurring in the jejunum of a 55-year-old man. The tumor was a polypoid 7.5-cm mass, which infiltrated the full thickness of the intestinal wall and the serosa of an adhesed loop of small bowel. On microscopic examination, the neoplasm was composed of sheets of spindle cells; focally, an anaplastic component was present, including tumor giant cells with bizarre nuclei. On immunohistochemical stains, tumor cells were positive for cytokeratin 7, cytokeratin AE1/AE3, vimentin, and focally, epithelial membrane antigen. No staining for cytokeratin 20 was found. Sarcomatoid carcinoma must be kept in mind in the differential diagnosis of malignant spindle cell tumors of the small bowel. As consensus regarding the terminology of these rare tumors is being reached, immunohistochemical stains are essential for accurate diagnosis

Arch Pathol Lab Med. 2004 Aug;128(8):918-21.

Adenocarcinoma of the small bowel: presentation, prognostic factors, and outcome of 217 patients.

METHODS: In the current study, the records of 217 patients with small bowel adenocarcinoma were reviewed retrospectively for the presentation, prognostic factors, treatment modalities, and outcome.

RESULTS: The median age of the patients was 55 years and there were 133 (61%) males. Tumors originated in the duodenum in 113 (52%) patients, the jejunum in 54 (25%) patients, the ileum in 28 (13%) patients, and in nonspecified sites in 22 (10%) patients. Patients with proximal tumors were diagnosed for the most part using endoscopy (i.e., 46 of 108 [43%]), whereas laparotomy enabled diagnosis in 16 of 28 (57%) patients with distal tumors. Based on TNM staging, 9 (4%) patients had Stage I disease, 43 (20%) patients had Stage II disease, 86 (39%) patients had Stage III disease, and 75 (35%) patients had Stage IV disease. The liver was the most common site of metastasis in 44 (59%) patients. Cancer-directed surgery was performed in 146 (67 %) patients, including the Whipple procedure in 36 patients (17%). The median overall survival time was 20 months. The 5-year overall survival rate was 26%. Cancer-directed surgery, early-stage disease, and lymph node involvement ratio were significantly associated with overall survival by univariate analysis. However, only cancer-directed surgery and lymph node involvement ratio were independent predictors of overall survival in a multivariate analysis (adjusted rate ratio = 0.14; 95% confidence interval [95% CI], 0.04-0.46; P = 0.001 and adjusted rate ratio = 0.25; 95% CI, 0.12-0.53; P < 0.001, respectively).

CONCLUSIONS: Performing an oncologic surgery resulted in the best outcome in patients with nonmetastatic disease. Because cancer-directed surgery is associated with high morbidity and mortality in primary centers, these patients should be referred to a tertiary center for adequate treatment.

Cancer. 2004; 101(3):518-26 **(ISSN: 0008-543X**

Table I Frequency of symptoms at presentation of small bowel adenocarcinoma

Symptom/Sign	Frequency (%)
Abdominal pain	42–83
Weight loss	23–87
Abdominal mass	19–29
Anemia	18–75
Nausea/Vomiting	27–34
Bleeding	13–68
Obstruction	16–65
Jaundice	18–30

Epidemiology

Frequency / United States

The incidence of small-bowel cancers in the United States in 2007 was projected to be 5640 cases, of which 2940 cases were projected to be in males and 2700 were projected to be in females. An estimated 1090 persons (males 570; females 520) were projected to die of the disease in 2007.

International

In general, prevalence is lower in Asia and in less industrialized countries than in Western countries.

Mortality/Morbidity

The 5-year overall survival rate for patients with adenocarcinoma has been estimated to be 30-35%.(Small-bowel sarcomas is approximately 25%.)

Race

According to one study, blacks have almost twice the incidence of carcinomas than whites do (10.6 versus 5.6 per million population).]

Sex

Men have higher rates of all types of small bowel cancer than women do, with a male-to-female ratio of 1.4:1.

Age

The prevalence of small-bowel cancer tends to increase with age, with a mean age at diagnosis of approximately 60 years.

American Cancer Society. Statistics for 200
Cancer Causes Control. 2005 Sep. 16(7):781-7.

Epidemiology

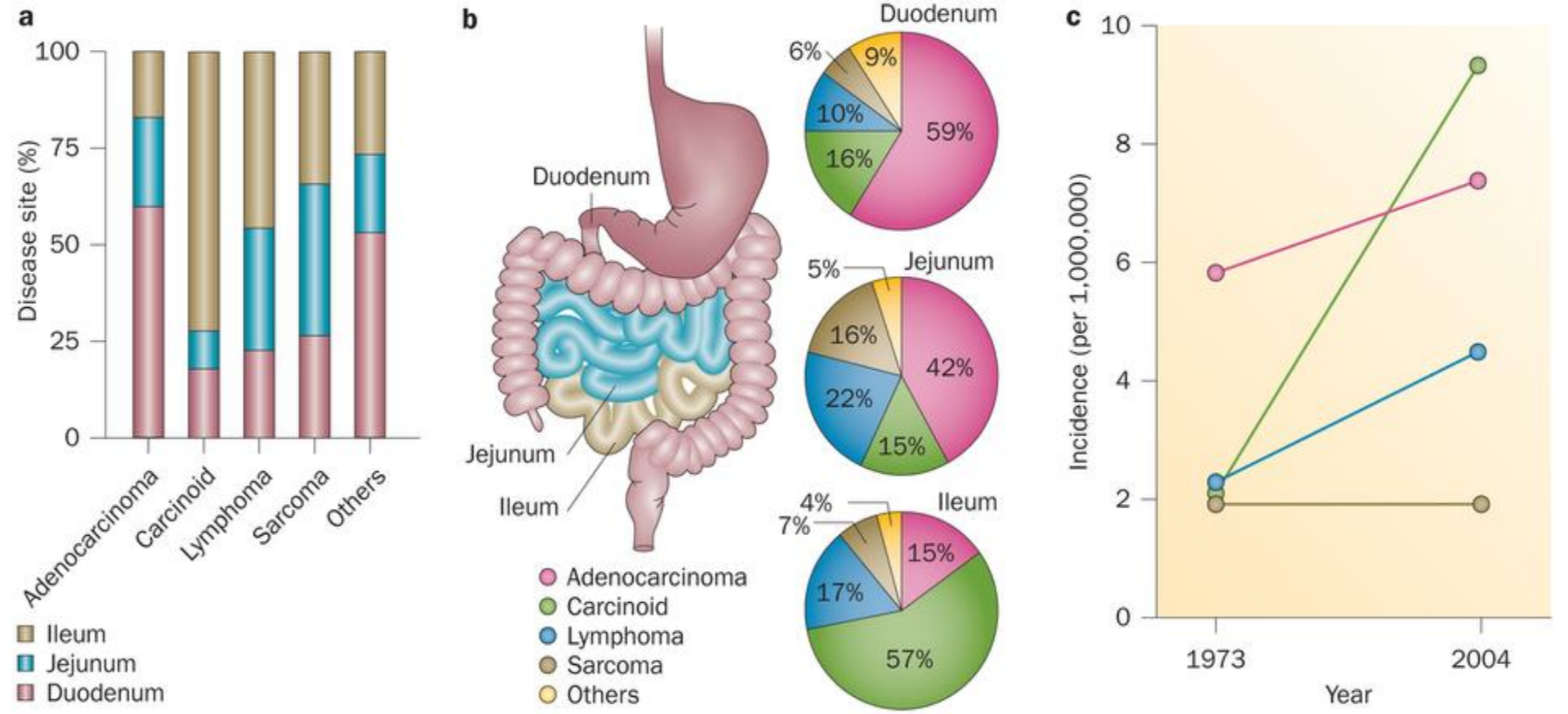
Despite the fact that the small intestine makes up 75% of the length of the digestive tract and 90% of its mucosal surface area, small bowel cancer is rare, accounting for less than 5% of gastrointestinal cancer].

According to the United States National Cancer Database, the incidence of all small bowel cancers in the USA rose from 11.8 cases/million persons in 1973 to 22.7 cases/million persons in 2004. Similarly, in France, their incidence also rose over the 1976–2001 period..

Small bowel adenocarcinoma (SBA) accounts for around 40% of all cancers of the small bowel; similarly, neuroendocrine tumours have roughly the same incidence. In the USA, the incidence of SBA has been estimated to be of 5300 new cases, with around 1100 deaths per year. The median age at diagnosis is in the sixth decade of life. According to the EUROCARE data, the estimated number of annual new cases of SBA in Europe is 3600 . The estimated incidence rate is 5.7 cases per million persons. In France the estimated incidence of SBA for the period 1989–2001 was 0.31/100,000 for men and 0.23/100,000 for women. According to the data from the Burgundy cancer registry, the number of new cases in France can be estimated to be 200 per year.

The duodenum is the most frequently involved segment, with 55–82% of cases, followed by the jejunum (11–25%) and ileum (7–17%)]. The increasing incidence of SBA is mainly due to the increase in duodenal tumours.

Digestive and Liver Disease, Volume 46, Issue 2, **February 2014, Pages 97–104**



Small bowel adenocarcinomas—existing evidence and evolving paradigms
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2013.132

Pathophysiology

Approximately 64% of all small-bowel tumors are malignant, and 40% of these tumors are adenocarcinomas.

Small-bowel adenocarcinomas are only one fiftieth(1/50) as common as large-bowel adenocarcinomas,

Small-bowel adenocarcinomas share a similar geographic distribution, with predominance in Western countries and co-occur in the same individuals, with an increased risk of small-bowel adenocarcinoma in survivors of colorectal cancer and vice versa.

Similar to the colon adenocarcinomas, they arise from adenomas with a stepwise accumulation of genetic mutations, become dysplastia→ carcinomas in situ → invasive carcinoma → metastasize via the lymphatics or portal circulation to the liver, lung, bone, brain, and other distant sites. This occurs both sporadically and in the context of familial adenomatous polyposis.

However, small-bowel adenocarcinomas tend to cluster away from the colon. 50% arise in the duodenum, 30% in the jejunum, and 20% in the ileum..

Predisposing Risk Factors for Small Intestine Cancer

Genetics predisposition gastrointestinal cancer sundromes:
Familial adenomatous polyposis,
Hereditary nonpolyposis colorectal cancer
Peutz-Jeghers syndrome

Other predisposition conditions
Crohn's disease
Celiac disease
Animal fat intake to be correlated with small-bowel cancer
Red meat, salt-cured and smoked foods raised the risk of cancer 2-3 times.
Tobacco and alcohol
Eating a high-fat diet.
Radiaton exposure
Males are 25% more likely to develop the disease

Cancer Lett. 1977 Jul. 3(1-2):83-6.
Cancer Causes Control. 1993 Mar. 4(2):163-9.
. *Cancer Epidemiol Biomarkers Prev*. 1994 Apr-May. 3(3):205-7
Cancer Epidemiol. 2015 Jun. 39 (3): 265-73.

Cancer Res. 2004 Oct 1. 64(19):7073-7. *Am. J. Gastroenterol.***100** (3): 703–10. doi:10.1111/j.1572-0241.2005

Predisposing Risk Factors for Small Intestine Cancer

2.4.1. Crohn's disease

Crohn's disease induces chronic inflammation in every segment of the digestive tract, and the distal ileum is the most frequently involved. The chronic inflammation releases cytokines that interact with cell surface receptors and target genes that can promote carcinogenesis.

The increased relative risk of SBA in Crohn's disease has been estimated in several population-based studies to range from 17 to 41 compared to the general population. The SBA arises in an inflamed small bowel segment. In contrast to sporadic SBA, in Crohn's disease, this cancer appears in younger patients (fourth decade of life), and mainly in the ileal segment.

The cumulative risk is estimated to be 0.2% after 10 years of Crohn's disease and 2.2% after 25 years.

Another estimation, based on the extensive SEER database and restricted to patients over 65 years old, identified 923 cases of small bowel cancer and 142,273 controls, and confirmed the increased risk of SBA in Crohn's disease (OR = 12.07; 95% CI, 6.07–20.80; $p < 0.001$). In this study, the prevalence of Crohn's disease in patients with small bowel cancer was low (1.6%); nevertheless many cases of SBA could have been missed in the SEER database as the median age of onset of SBA in Crohn's disease patients is less than 65 years.

Another study suggests that patients who have undergone a small bowel resection or prolonged treatment with salicylate have a lower risk of developing SBA.

Predisposing Risk Factors for Small Intestine Cancer

2.4.2. Coeliac disease

Coeliac disease is characterised by a lymphocytic infiltrate that induces immunological disruption and damage to the epithelial cells that can include premalignant changes, and could increase the risk of both SBA and small bowel lymphoma. A cohort of 235 patients with coeliac disease showed an 8% prevalence of SBA. In a British survey study that included 395 cases of small bowel cancer (107 lymphomas, 175 SBAs and 79 neuroendocrine tumours), coeliac disease was found in 13% of cases of SBA and 39% of cases of lymphoma; primary location of SBA was usually jejunal. In a Swedish registry study, the relative risk of SBA in patients with coeliac disease versus the general population was estimated to be 10.

The preliminary results of the French NADEGE cohort that prospectively included 127 patients with SBA from March 2009 to September 2010, revealed a genetic syndrome or a predisposing disease in 20% of the patients: Crohn's disease (8.6%), FAP (3%), Lynch syndrome (3%), coeliac disease (1.5%) and Peutz–Jeghers syndrome (0.8%) (7). These preliminary results indicate that a predisposing disease or genetic syndrome is considerably more frequent in SBA than in colorectal cancer.

Predisposing Risk Factors for Small Intestine Cancer

Genetic risk factors

Familial adenomatous polyposis: After the colon, the duodenum is the most common site of adenocarcinoma and have a relative risk of more than 300 times but no elevated risk for gastric or nonduodenal small-bowel cancer. A high frequency of p53 overexpression in dysplastic adenomas, although the frequency of*TP53* and k-*ras* gene mutations was much lower.[13]

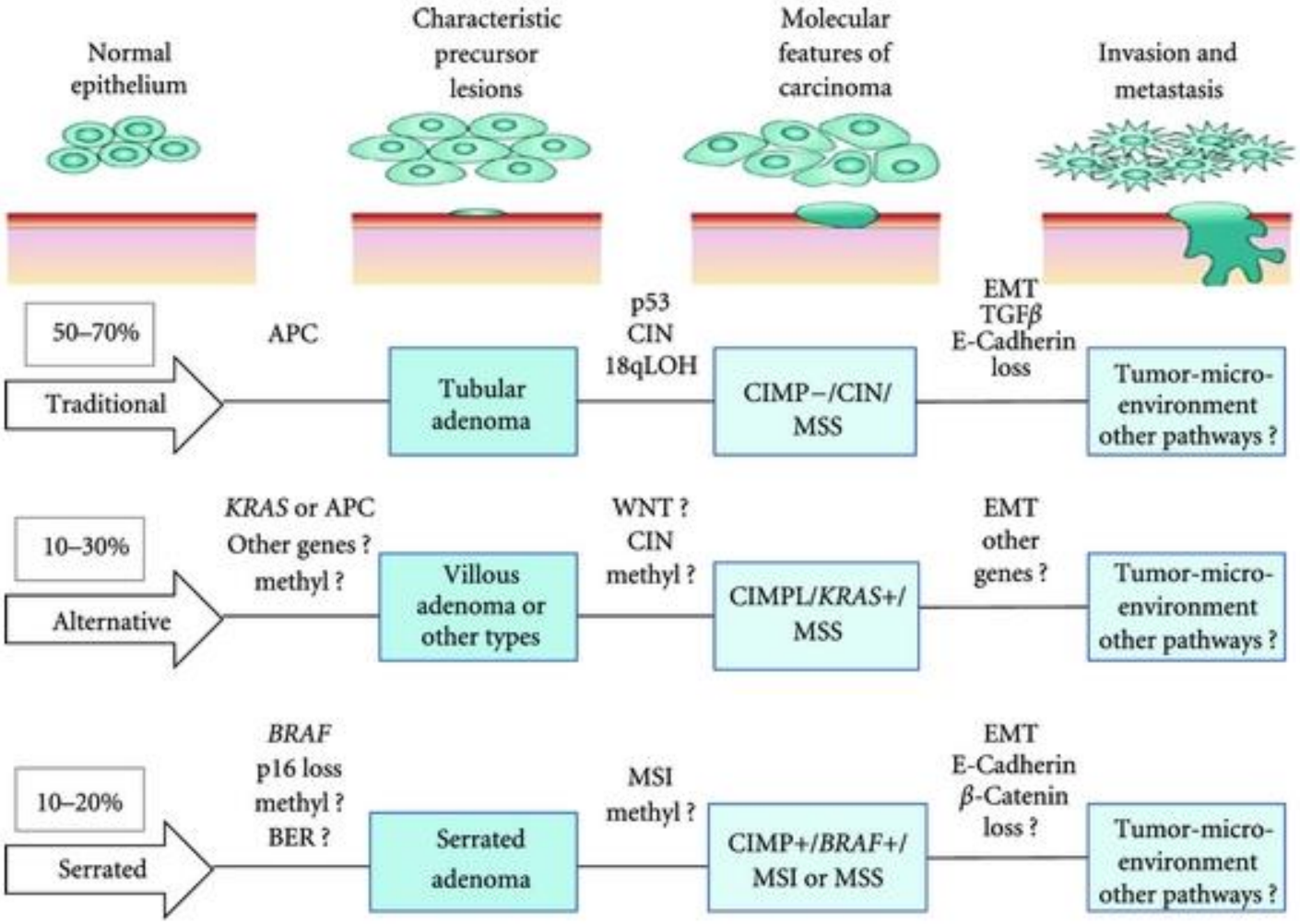
Hereditary nonpolyposis colorectal cancer: Aside from colorectal carcinoma, patients with this genetic syndrome also develop endometrial, gastric, small bowel, upper urinary tract, and ovarian carcinomas. The lifetime risk of small-bowel adenocarcinoma in patients with hereditary nonpolyposis colorectal cancer is 1-4%, which is more than 100 times the risk in the general population. They occur at younger age and appear to have a better prognosis than sporadic cases. The most commonly mutated genes are *HMLH1* and *HMSH2*, which are involved in DNA mismatch repair.

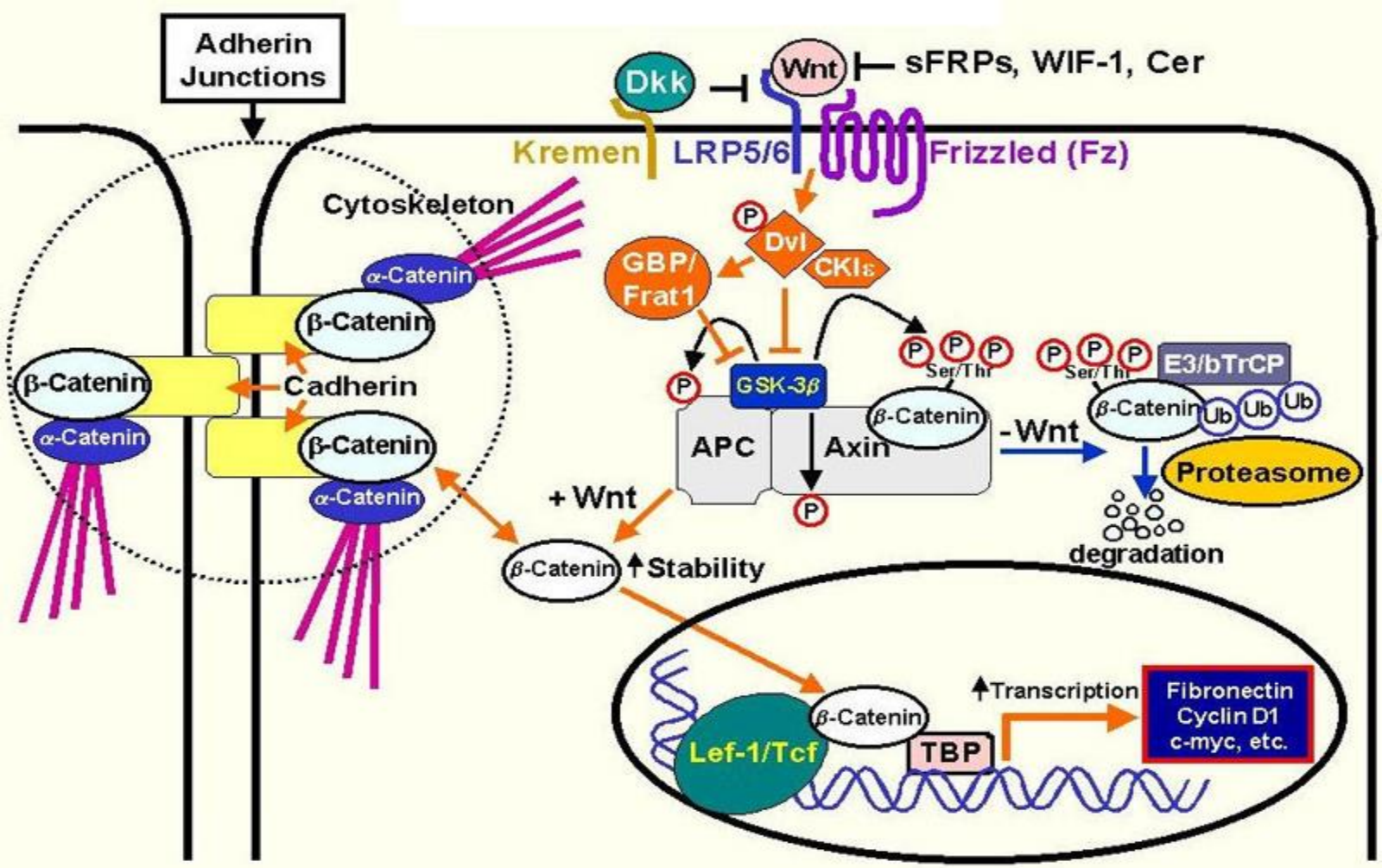
Peutz-Jeghers syndrome: Hemminki has reported an approximately 18-fold increase in the incidence compared to that in the general population.

Clin Lab Med. 2013 Dec. 33(4):861-6. .
Gastroenterology. 1992 Jun. 102(6):1980-2.
Br J Surg. 1997 Jun. 84(6):826-9.

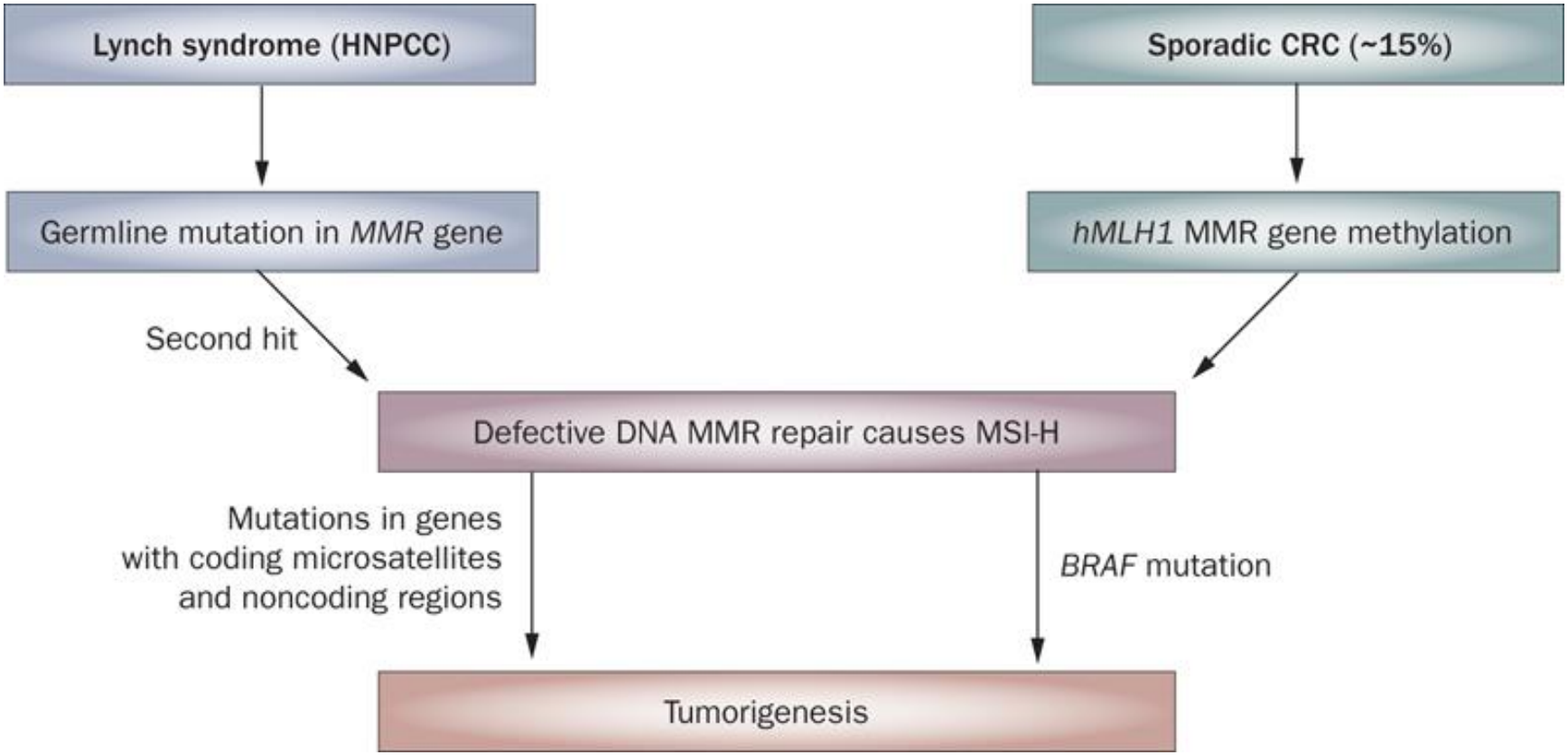
MOLCULAR CHANGES IN SMALL BOWEL ADENOCARCINOMA

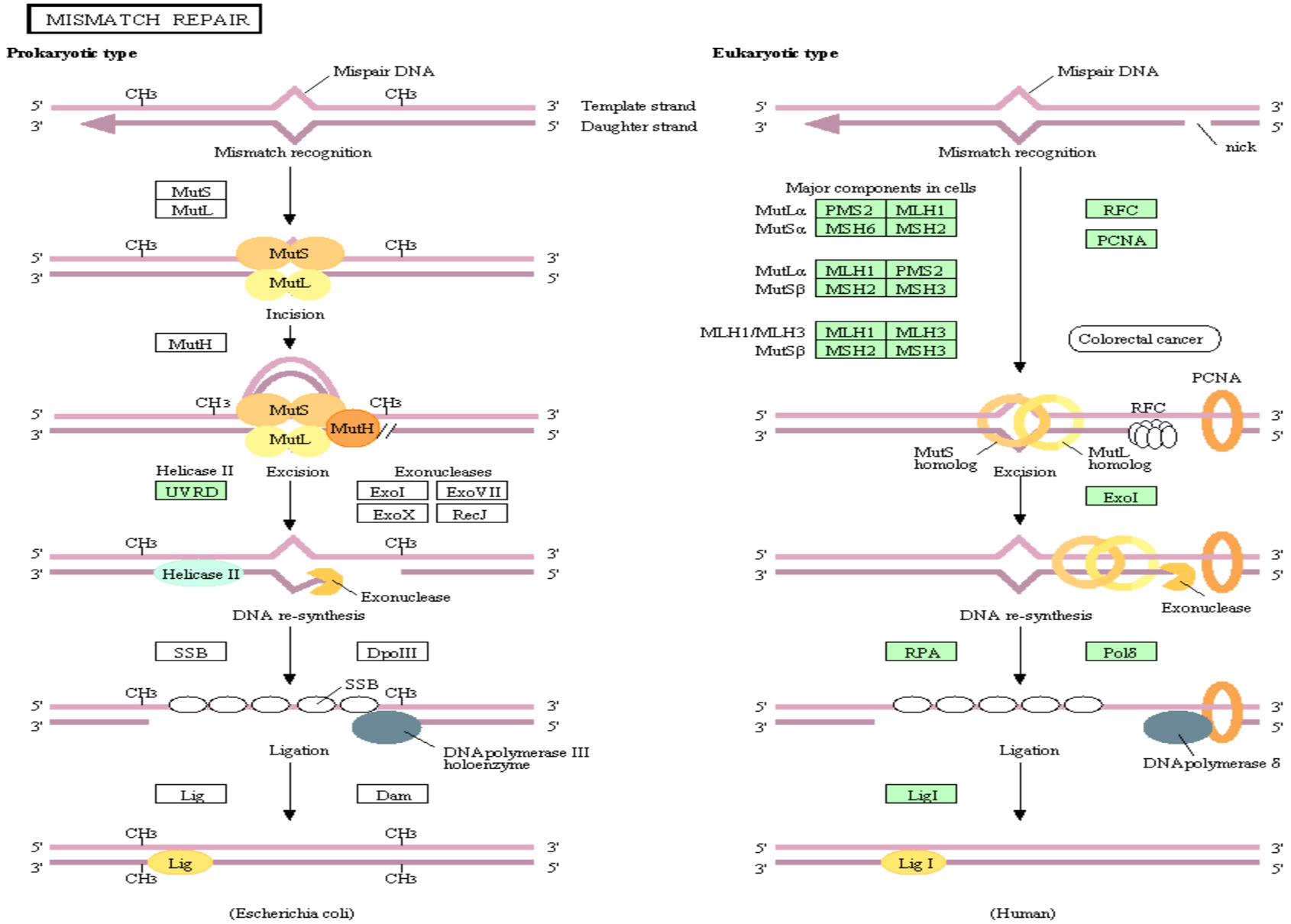
Reference	of patients	Abnormal P53	β-CATENIN	HER2 over-expression	APC mutation	*KRAS* mutation	dMMR phenotype
Wheeler et al. [18]	21	24%	48%	–	0%	–	5%
Arai et al. [19]	15	27%	–	–	8%	53%	–
Blaker et al. [20]	17	–	–	–	18%	–	12%
Aparicio et al. [21]	63	42%	20%	3.9%	–	43%	14%
Svrcek et al. [23]	27	52%	7.4%	–	–	–	7%
Overman et al. [24]	54	–	–	1.7%	–	–	35%
Blaker et al. [25]	21	–	24%	–	10%	57%	–
Planck et	89	–	–	–	–	–	18%

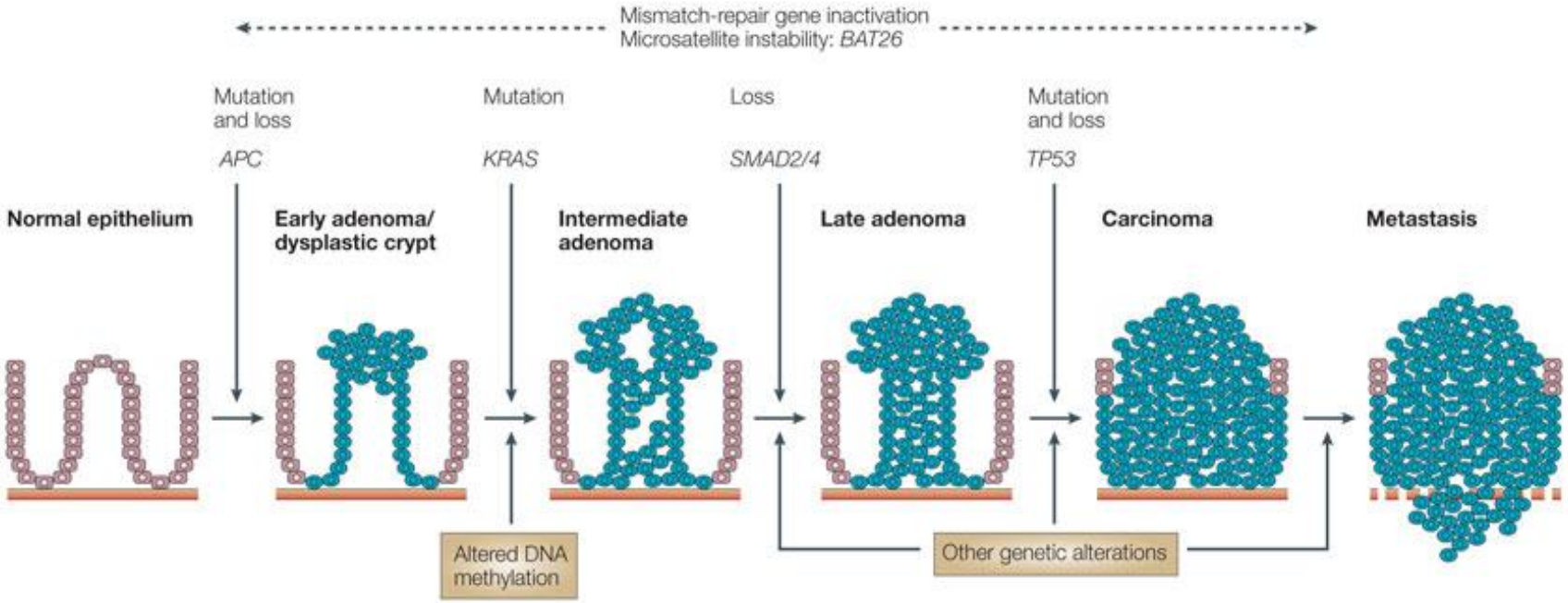

Normal epithelium
Characteristic precursor lesions
Molecular features of carcinoma
Invasion and metastasis
50–70%
Traditional
APC
Tubular adenoma
p53
CIN
18qLOH
CIMP−/CIN/ MSS
EMT
TGFβ
E-Cadherin loss
Tumor-micro-environment other pathways ?
10–30%
Alternative
KRAS or APC
Other genes ?
methyl ?
Villous adenoma or other types
WNT ?
CIN
methyl ?
CIMPL/KRAS+/ MSS
EMT
other genes ?
Tumor-micro-environment other pathways ?
10–20%
Serrated
BRAF
p16 loss
methyl ?
BER ?
Serrated adenoma
MSI
methyl ?
CIMP+/BRAF+/ MSI or MSS
EMT
E-Cadherin
β-Catenin
loss ?
Tumor-micro-environment other pathways ?



- The embryonic processes it controls include body axis patterning, cell fate specification, cell proliferation and cell migration. Wnt signaling also controls tissue regeneration in adult bone marrow, skin and intestine.
- This pathway's was demonstrated that lead to breast and prostate cancer, glioblastoma, type II diabetes and others.


Lynch syndrome (HNPCC)
Sporadic CRC (~15%)
Germline mutation in *MMR* gene
hMLH1 MMR gene methylation
Second hit
Defective DNA MMR repair causes MSI-H
Mutations in genes with coding microsatellites and noncoding regions
BRAF mutation
Tumorigenesis




Mismatch-repair gene inactivation
Microsatellite instability: BAT26
Mutation and loss
APC
Mutation
KRAS
Loss
SMAD2/4
Mutation and loss
TP53
Normal epithelium
Early adenoma/ dysplastic crypt
Intermediate adenoma
Late adenoma
Carcinoma
Metastasis
Altered DNA methylation
Other genetic alterations

Mutations of the Ki-ras, p53 and APC genes in adenocarcinomas of the human small intestine.

- In contrast to the origins of colorectal carcinomas, the mechanisms of carcinogenesis in the small intestine remain unclear. We therefore analyzed the mutational status of the Ki-ras, p53, and adenomatous polyposis coli (APC) genes in primary carcinomas of the small intestine and compared the mutation patterns with those established for colorectal cancers. DNA was extracted from 15 formalin-fixed, paraffin-embedded lesions. Codons 12, 13 and 61 of the Ki-ras gene, exons 5-8 of the p53 gene, and codons 1268-1569, which contain the mutation cluster region (MCR) of the APC gene, were amplified by means of PCR, subcloned and sequenced. Mutations of the Ki-ras and p53 genes were observed in 8 (53.3%) and 4 lesions (26.7%), respectively. The mutational frequency of the Ki-ras gene in the present series of small intestinal carcinomas was similar, while that of the p53 gene was slightly lower than the reported frequencies for colorectal carcinomas. Only one case showed a mutation of the APC gene, involving an insertional mutation of an adenine at codons 1554-1556 with formation of a stop codon immediately downstream. Since the occurrence of an APC mutation is considered an early event in colorectal carcinogenesis, our findings indicating an extremely low frequency of such changes in and around the MCR suggest that carcinomas of the small intestine arise via a genetic pathway distinct from that involved in the development of carcinomas of the colorectum
- **Int J Cancer. 1997; 70(4):390-5 (ISSN: 0020-7136)**

An insight into the genetic pathway of adenocarcinoma of the small intestine.

SUBJECTS AND METHODS: A total of 21 non-familial, non-ampullary adenocarcinomas of the small intestine were analysed. DNA was extracted from formalin fixed paraffin wax embedded tissue using standard techniques. The replication error (RER) status was determined by amplification of BAT26. The mutation cluster region (MCR) of the adenomatous polyposis coli (APC) gene was screened using polymerase chain reaction single strand conformational polymorphism and direct sequencing. Immunohistochemistry was performed on formalin fixed paraffin wax embedded tissue using monoclonal antibodies for hMLH1, hMSH2, beta-catenin, E-cadherin, and p53.

RESULTS: Fourteen male and seven female patients with a median age of 64 years (range 21-85) presented with adenocarcinoma of the duodenum (10), jejunum (7), and ileum (4). One cancer (5%) was found to be RER+, and all tumours stained positive for hMLH1 and hMSH2. No mutations were detected in the MCR of the APC gene. beta-Catenin showed increased nuclear expression with loss of membranous staining in 10 cancers (48%). Absent or decreased membrane expression of E-cadherin was found in eight cancers (38%). Strong staining of p53 was found in the nucleus of five cancers (24%).

CONCLUSION: We did not detect mutations in the MCR of the APC gene, and this suggests that adenocarcinoma of the small intestine may follow a different genetic pathway to colorectal cancer. Abnormal expression of E-cadherin and beta-catenin was common and reflects an early alternative to APC in this pathway in which mutations may be found in adenocarcinoma of the small intestine.

Gut. 2002; 50(2):218-23 (ISSN: 0017-5749)

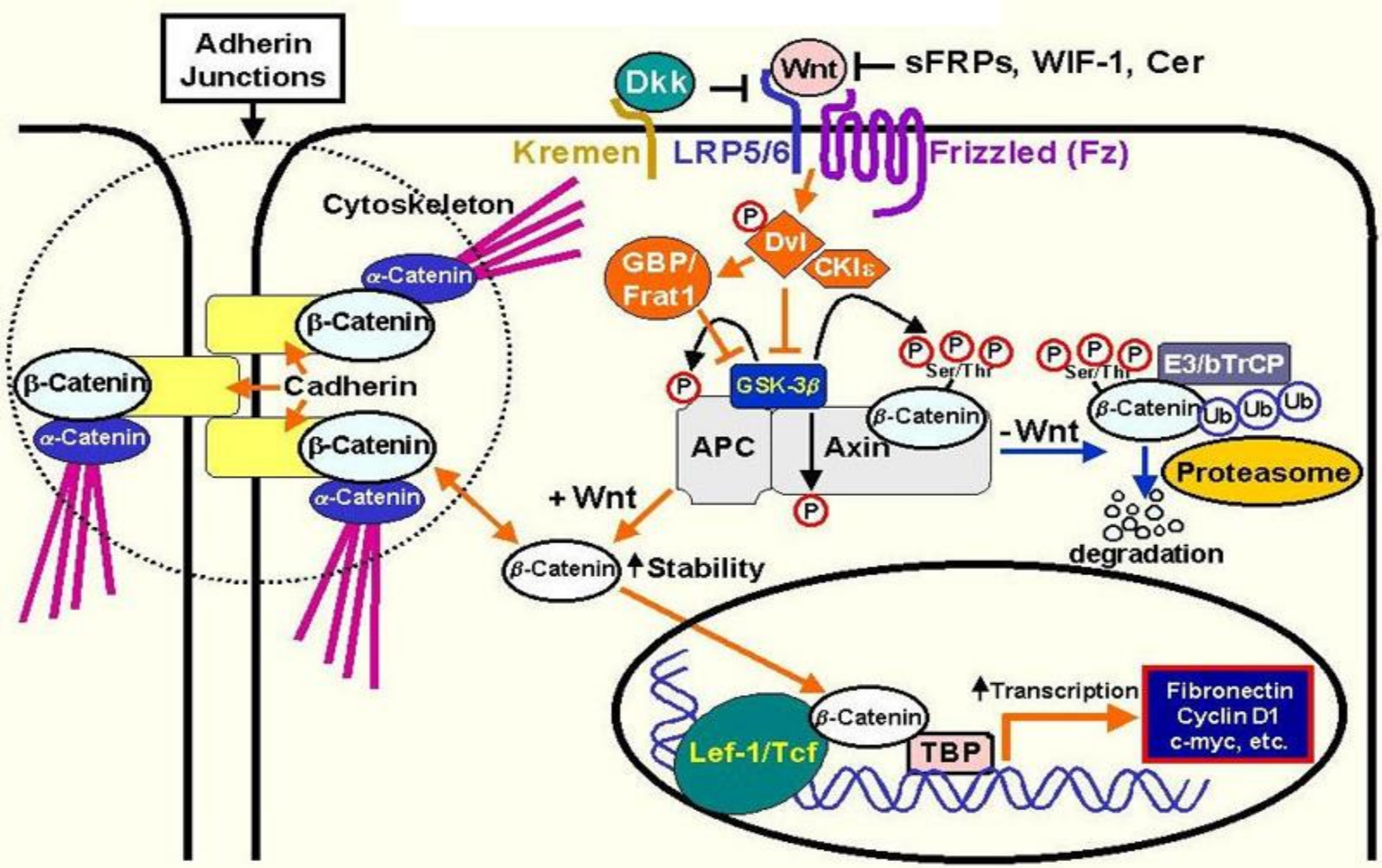
Immunohistochemical analysis of adenocarcinoma of the small intestine: a tissue microarray study.

METHODS: Twenty seven primary sporadic small intestinal adenocarcinomas were analysed. The TMA technique was validated by comparing immunohistochemical labelling of hMLH1 and hMSH2 on TMAs and the tissue sections they derived from. The expression of Smad4, hMSH6, beta catenin, and p53 was investigated and results compared with those obtained in 14 malignant ampullary tumours.

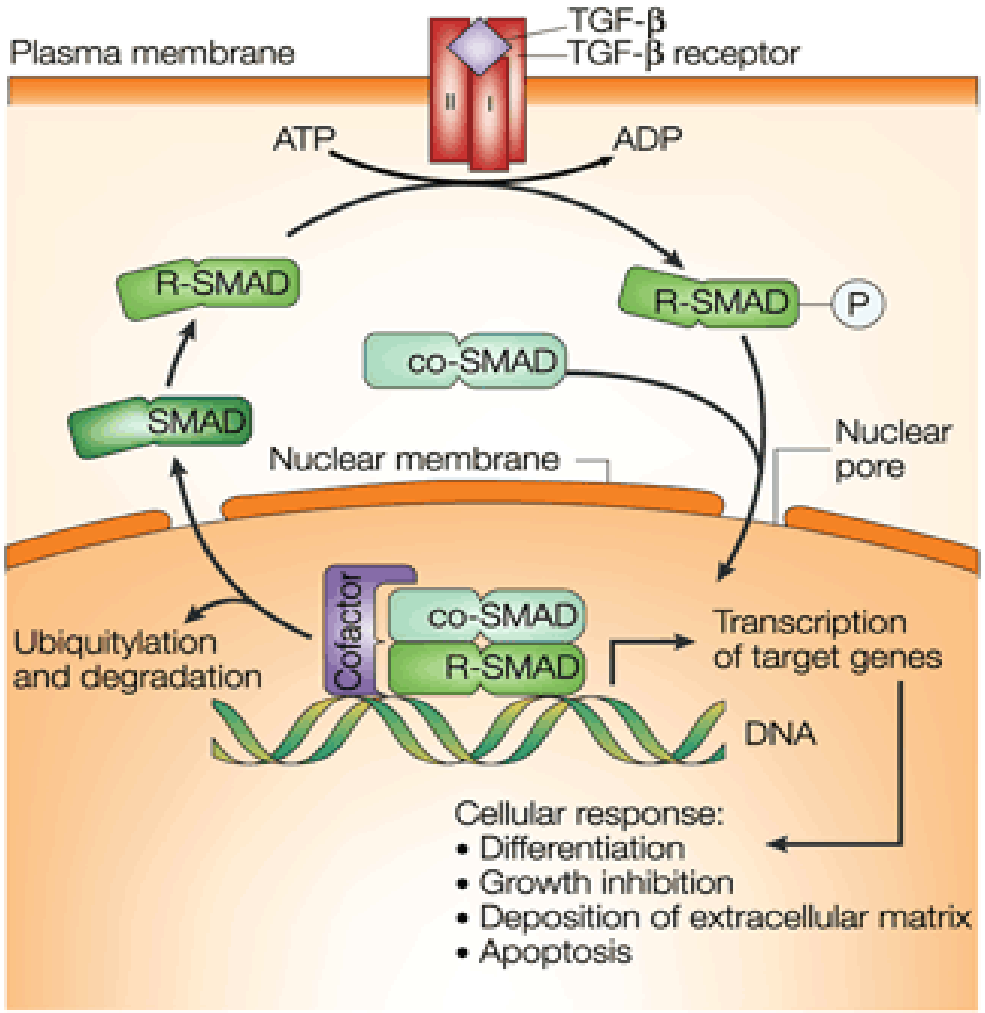
RESULTS: TMA technology with threefold redundancy adequately represented the immunohistochemical pattern of small intestinal adenocarcinomas. Loss of hMLH1 expression, but not hMSH2 or hMSH6, was seen in two of 27 small intestinal adenocarcinomas. All ampullary tumours showed nuclear staining for hMSH2 and hMSH6. One case showed lack of immunostaining for hMLH1. Smad4 expression was absent in five small intestinal adenocarcinomas and two ampullary tumours. Overexpression of p53 was detected in the nuclei of 14 of the 27 small intestinal adenocarcinomas, and five of the 14 ampullary tumours. Nuclear or cytoplasmic expression of beta catenin was present in all specimens.

CONCLUSION: Inactivation of the SMAD4/DPC4 gene seems to be involved in small intestinal adenocarcinoma tumorigenesis. Overexpression of p53 and abnormal expression of beta catenin are two common events, unlike the loss of expression of the DNA mismatch repair proteins (hMLH1, hMSH2, and hMSH6). The carcinogenetic process appears to be similar in small intestinal adenocarcinomas and malignant ampullary tumours.

J Clin Pathol. 2003; 56(12):898-903 (ISSN: 0021-9746)



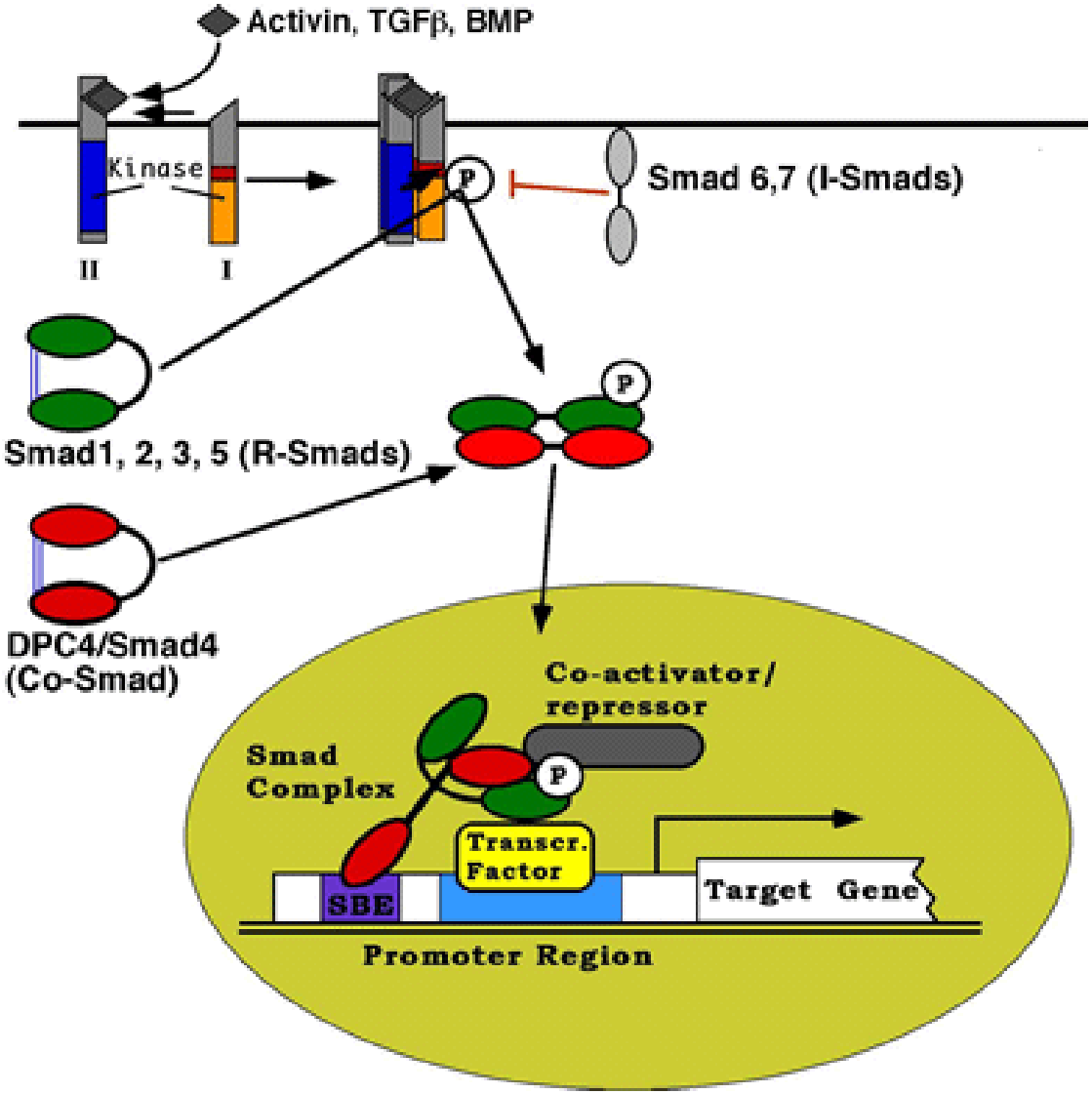
- The embryonic processes it controls include body axis patterning, cell fate specification, cell proliferation and cell migration. Wnt signaling also controls tissue regeneration in adult bone marrow, skin and intestine.
- This pathway's was demonstrated that lead to breast and prostate cancer, glioblastoma, type II diabetes and others.



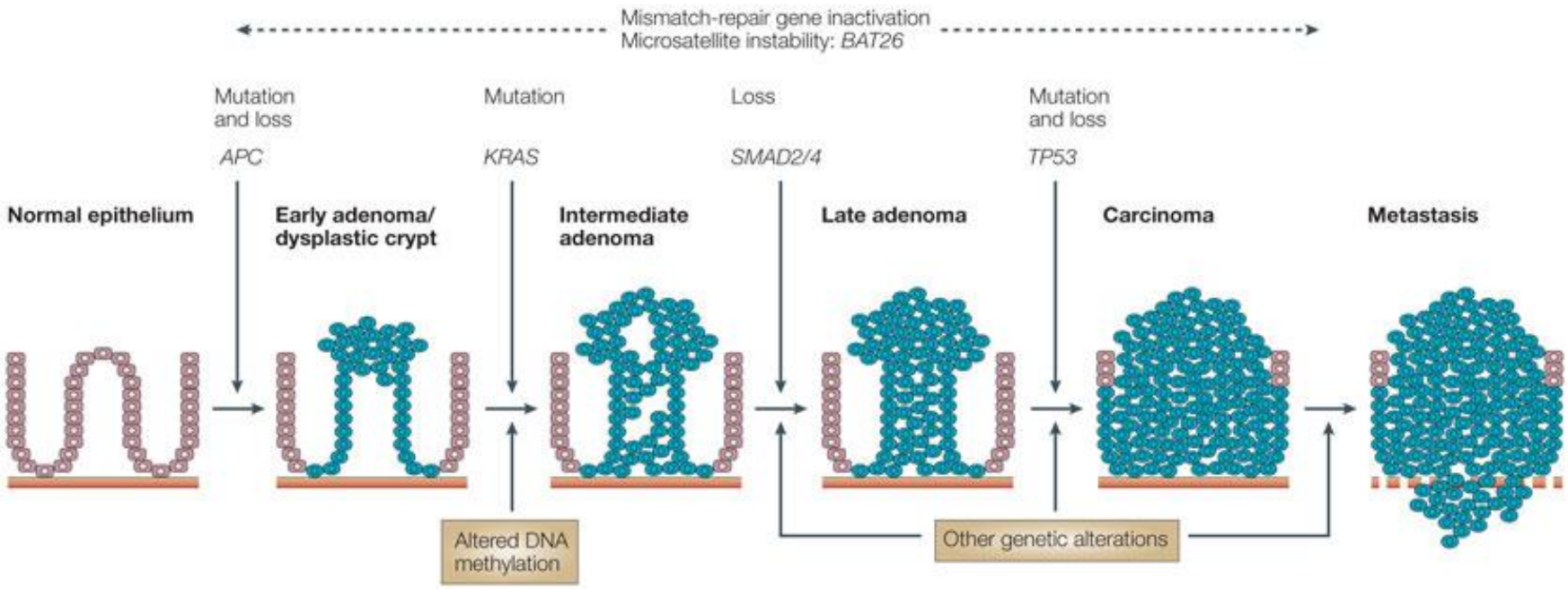
Nature Reviews | Cancer

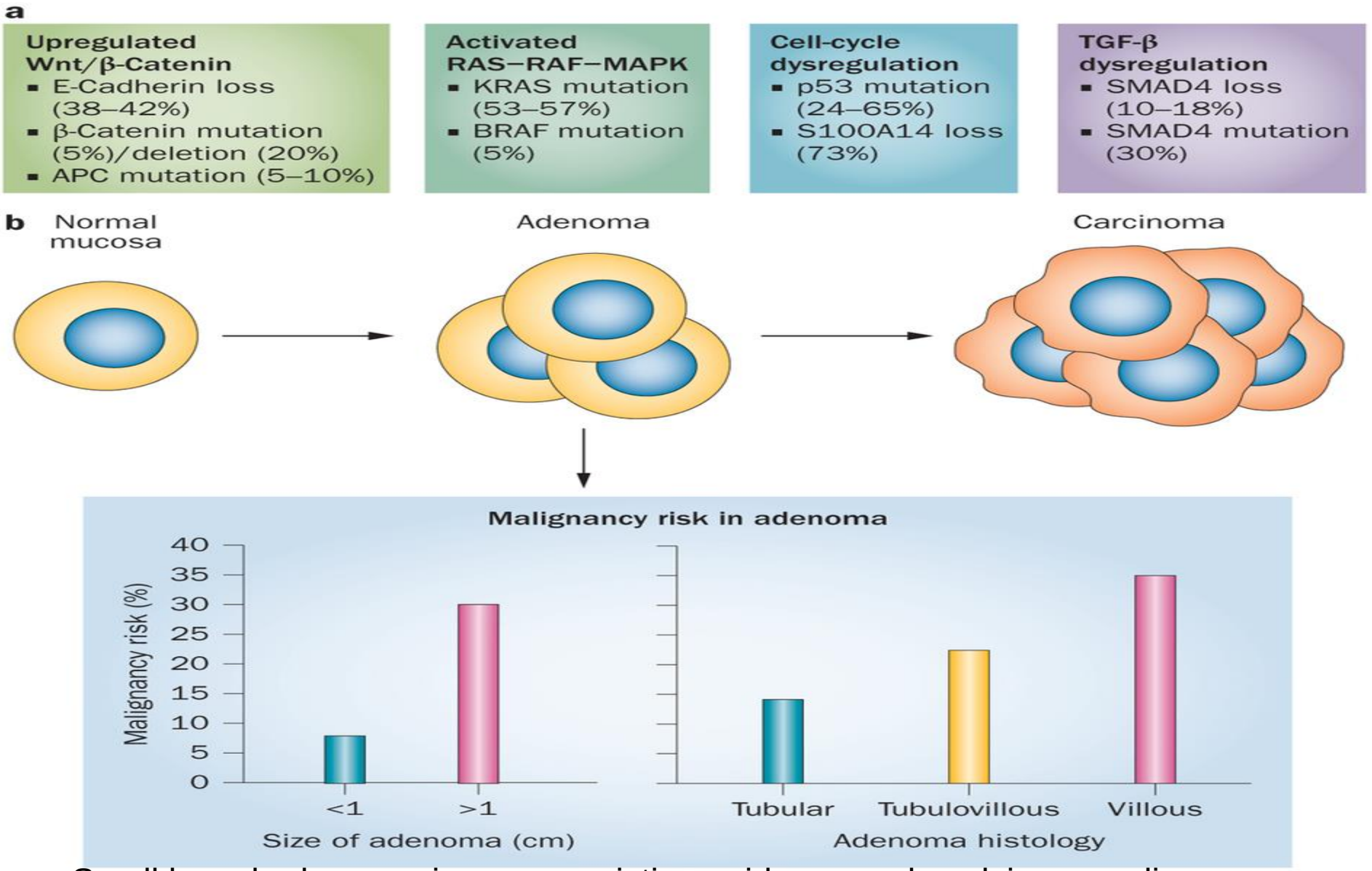
Smad4 is a key mediator of the TGF-β pathway,

and is mutated and/or deleted in many cancers.



- The SMAD proteins are homologs of both the *Drosophila* protein MAD and the *C. elegans* protein SMA


Mismatch-repair gene inactivation
Microsatellite instability: BAT26
Mutation and loss
APC
Mutation
KRAS
Loss
SMAD2/4
Mutation and loss
TP53
Normal epithelium
Early adenoma/ dysplastic crypt
Intermediate adenoma
Late adenoma
Carcinoma
Metastasis
Altered DNA methylation
Other genetic alterations



Small bowel adenocarcinomas—existing evidence and evolving paradigms
Nat. Rev. Clin. Oncol. doi:10.1038/nrclinonc.2013.132

The genetic pthway of adenocarcinoma of the small intestine.

Abnormal expression of E-cadherin and beta-catenin was common and reflects an early alternative to APC pathway in adenocarcinoma of the small intestine

K-ras mutation and p53 overexpression appear to be as common in small-bowel as in colorectal adenocarcinomas.

The *SMAD4/DPC4* gene, which is often mutated in pancreatic and colorectal carcinomas, also appears to be inactivated in small-bowel adenocarcinomas

APC tumor suppressor gene, which is characteristic of colorectal carcinoma, does not commonly occur in small-bowel

Oncogene. 2002 Jan 3. 21(1):158-64.

MOLCULAR CHANGES IN SMALL BOWEL ADENOCARCINOMA

Reference	of patients	Abnormal P53	β-CATENIN	HER2 over-expression	APC mutation	*KRAS* mutation	dMMR phenotype
Wheeler et al. [18]	21	24%	48%	–	0%	–	5%
Arai et al. [19]	15	27%	–	–	8%	53%	–
Blaker et al. [20]	17	–	–	–	18%	–	12%
Aparicio et al. [21]	63	42%	20%	3.9%	–	43%	14%
Svrcek et al. [23]	27	52%	7.4%	–	–	–	7%
Overman et al. [24]	54	–	–	1.7%	–	–	35%
Blaker et al. [25]	21	–	24%	–	10%	57%	–
Planck et	89	–	–	–	–	–	18%

Distribution of primary neoplasms in the small intestine from an analysis of 67,843 patients from the National Cancer Database (1985-2005)

Location	Primary neoplasms of the SI (%)			
	Carcinoid Tumor*	Adenocarcinoma	Lymphoma	Sarcoma*
Duodenum	18	56	18	16
Jejunum	6	16	16	25
Ileum	45	13	21	15
Overlapping disease or location not specified	32	15	46	44

SI: small intestine.

* Percentages were rounded, so total exceeds 100.

Reference:

1. *Bilimoria KY, Bentrem DJ, Wayne JD, et al. Small bowel cancer in the United States: changes in epidemiology, treatment, and survival over the last 20 years. Ann Surg 2009; 249:63.*

Predisposing Risk Factors for Small Intestine Cancer

Genetic predisposition

2.3.1. Familial adenomatous polyposis (FAP)

FAP is a consequence of a germinal mutation of the *APC* gene. FAP patients are exposed to a very high incidence of colorectal cancer at a young age, and SBA is the second most common primary cancer location.

In a pooled registry study of 1255 patients with FAP, 57 (4.5%) had an upper digestive tract adenocarcinoma. The primary location was the duodenum in 29 cases (50%), the ampulla of Vater in 10 (18%), the stomach in 7 (12%), the jejunum in 5 (8.5%), and the ileum in 1 case (1.7%).

In another study, the relative risks for duodenal adenocarcinoma or ampulloma in a FAP patient compared to those in the general population were 330 (95% CI, 132–681; $p < 0.001$), and 123 (95% CI, 33–316; $p < 0.001$), respectively. Even though the risk of duodenal adenocarcinoma in a FAP patient remained less than 5%, this cancer is nevertheless the main cause of cancer-related death in patients who have undergone a coloproctectomy.

Predisposing Risk Factors for Small Intestine Cancer

2.3.2. Lynch syndrome

Lynch syndrome is caused by a germline mutation of a DNA mismatch repair gene, which exposes the patient to various types of neoplasia, such as colorectal and endometrial cancers; the less frequently ovarian, urothelial, gastric, biliary tract cancers and SBA.

According to data from a Dutch study, the relative risk of SBA for a patient with Lynch syndrome has been estimated to range from 25 in the early phases of the syndrome to 291 (95% CI, 71–681) in case of an *MLH1* mutation and 103 (95% CI, 14–729) in case of an *MSH2* mutation .

Nevertheless, the lifetime cumulative risk remains low: 0.6% and 1% according to Finnish and French registries, respectively and. So far, it has not been recommended to screen Lynch syndrome patients for SBA. However, analysis of the MMR phenotype is systematically recommended in SBA, because it could reveal the presence of Lynch syndrome and.

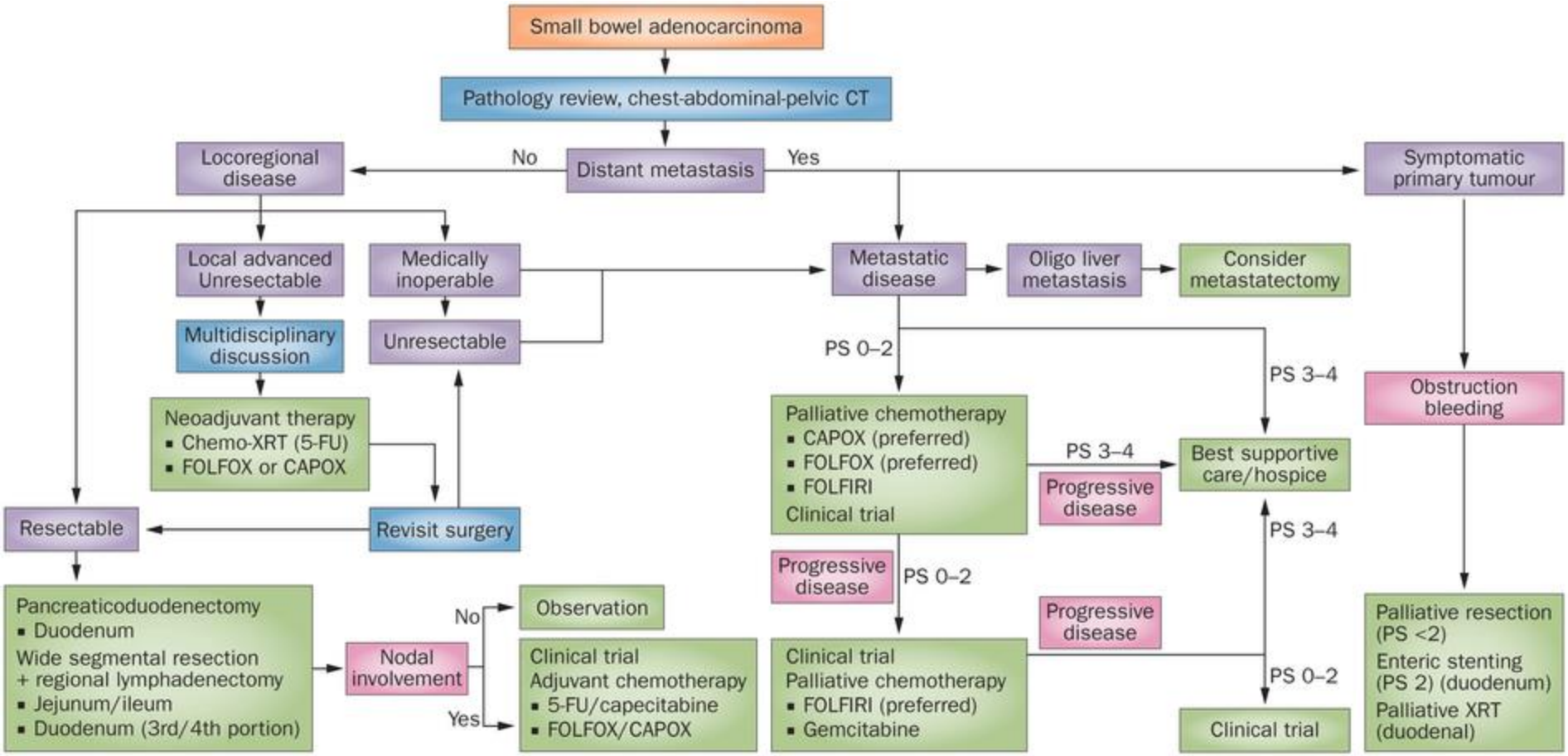
Predisposing Risk Factors for Small Intestine Cancer

2.3.3. Peutz–Jeghers syndrome

The Peutz–Jeghers syndrome is an autosomal dominant disorder due to the *STK11* suppressor gene mutation that predisposes to hamartomatous gastrointestinal tract polyposis.

A relative risk of 520 (95% CI, 220–1306) for SBA was observed in Peutz–Jeghers syndrome patients. The adenocarcinoma probably originates from the intra-epithelial neoplasia observed in the hamartomatous lesion.

E. coli	*S. cerevisiae*	Human	Functions of Eukaryotic Proteins
MutS	MSH2	MSH2	MutSα (with MSH6; 80-90%); MutSβ (with MSH3)
"	MSH3	MSH3	MutSβ (with MSH2); repair of larger loops
"	MSH6	MSH6	MutSα (with MSH2); repair of mismatches and small loops
MutL	MLH1	MLH1	Forms heterodimers with the other three MutL homologs
"	PMS1	PMS2	MutLα (90%); Mismatch repair; endonuclease motif
"	MLH2	PMS1	MutLβ; Role unknown
"	MLH3	MLH3	MutLγ; Mismatch repair; endonuclease motif
MutH	?	?	?
uvrD	?	?	?
?	Exonuclease I	Exonuclease I	Excision (5' to 3' polarity)
?	RFC, PCNA, Polγ	RFC, PCNA, Polγ	Nick identification; gap filling



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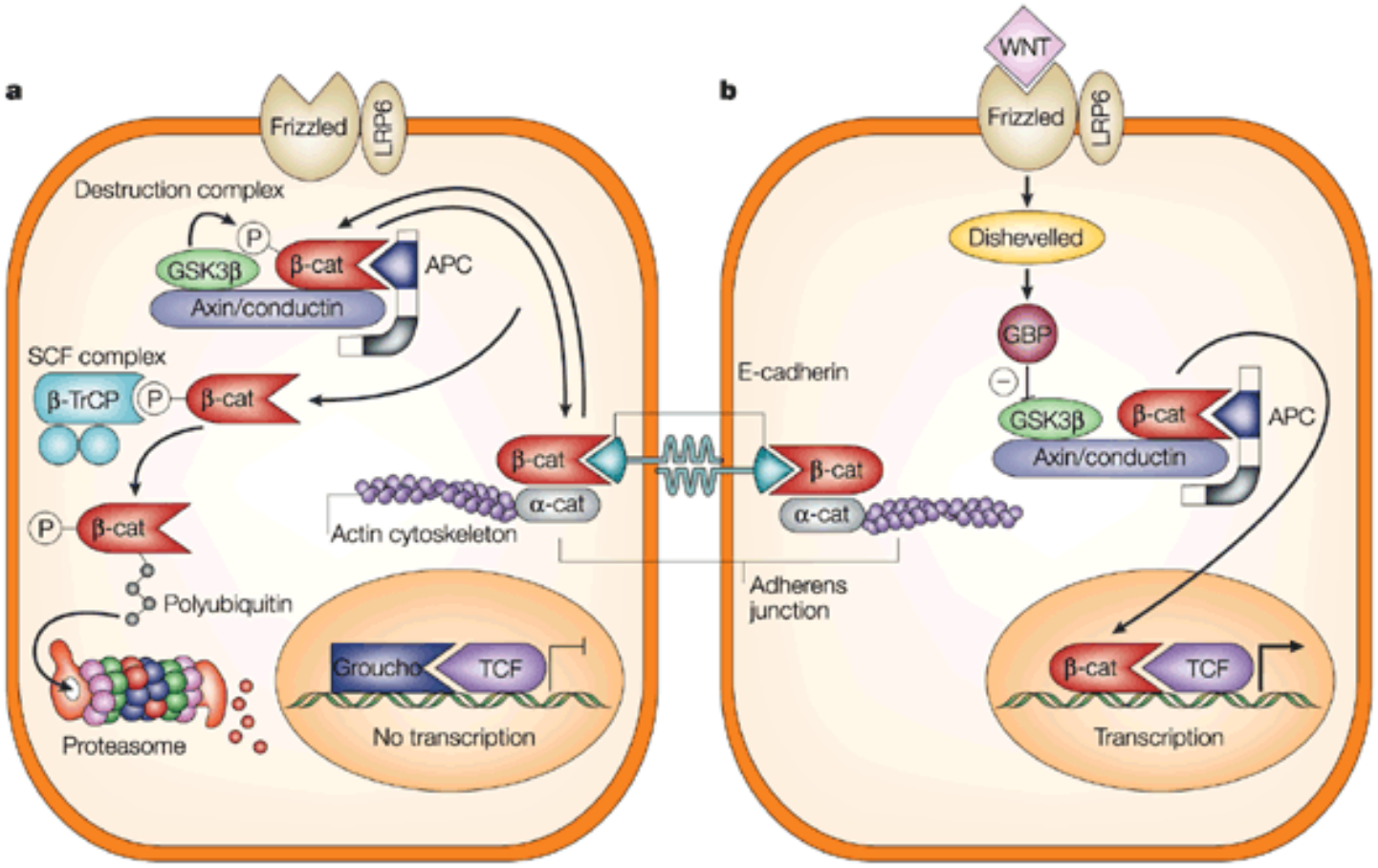
a
Frizzled
LRP6
Destruction complex
P
GSK3β
β-cat
APC
Axin/conductin
SCF complex
β-TrCP
P
β-cat
P
β-cat
Polyubiquitin
Proteasome
β-cat
α-cat
Actin cytoskeleton
Groucho
TCF
No transcription
E-cadherin
β-cat
α-cat
Adherens junction
b
WNT
Frizzled
LRP6
Dishevelled
GBP
GSK3β
β-cat
APC
Axin/conductin
β-cat
TCF
Transcription

Repair System	Enzymes/proteins	Repair System	Enzymes/proteins
Base excision	DNA glycosylase	Mismatch	Dam methylase
	AP endonuclease		MutS, MutL, MutH
	DNA polymerase I		Exonuclease
	DNA ligase		DNA helicase II
Nucleotide excision	Uvr-A, Uvr-B, Uvr-C		SSB protein
	DNA polymerase I		DNA polymerase III
	DNA ligase		DNA ligase

E. coli	*S. cerevisiae*	Human	Functions of Eukaryotic Proteins
MutS	MSH2	MSH2	MutSα (with MSH6; 80-90%); MutSβ (with MSH3)
"	MSH3	MSH3	MutSβ (with MSH2); repair of larger loops
"	MSH6	MSH6	MutSα (with MSH2); repair of mismatches and small loops
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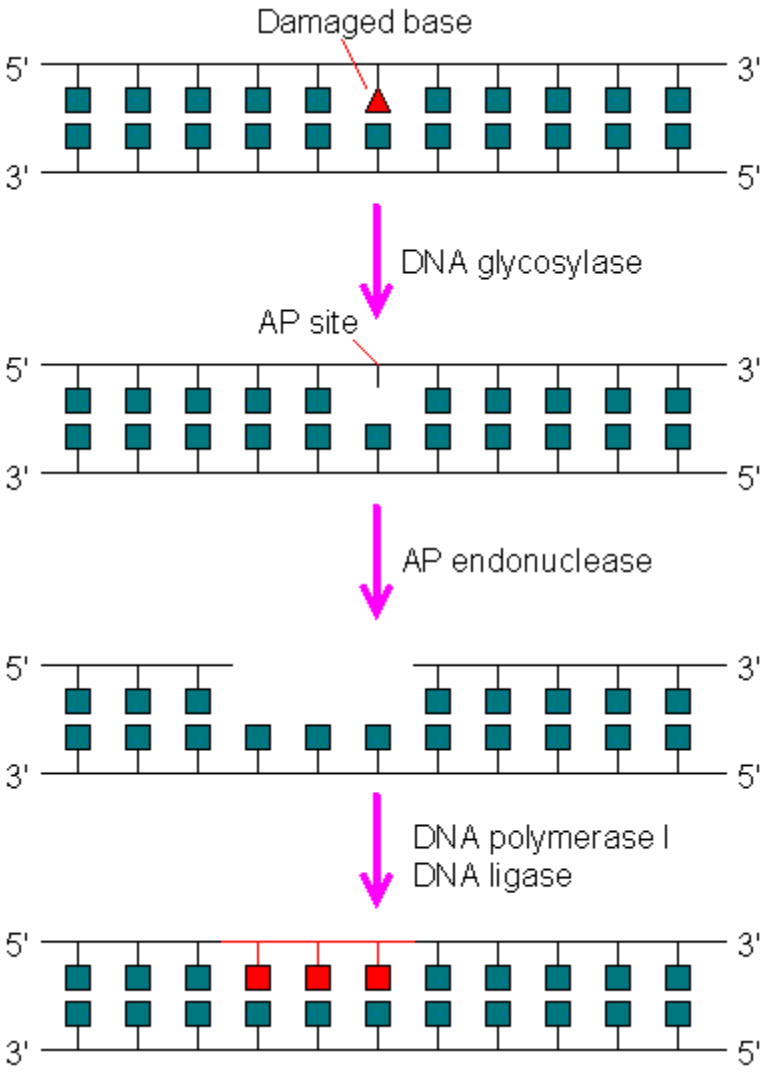
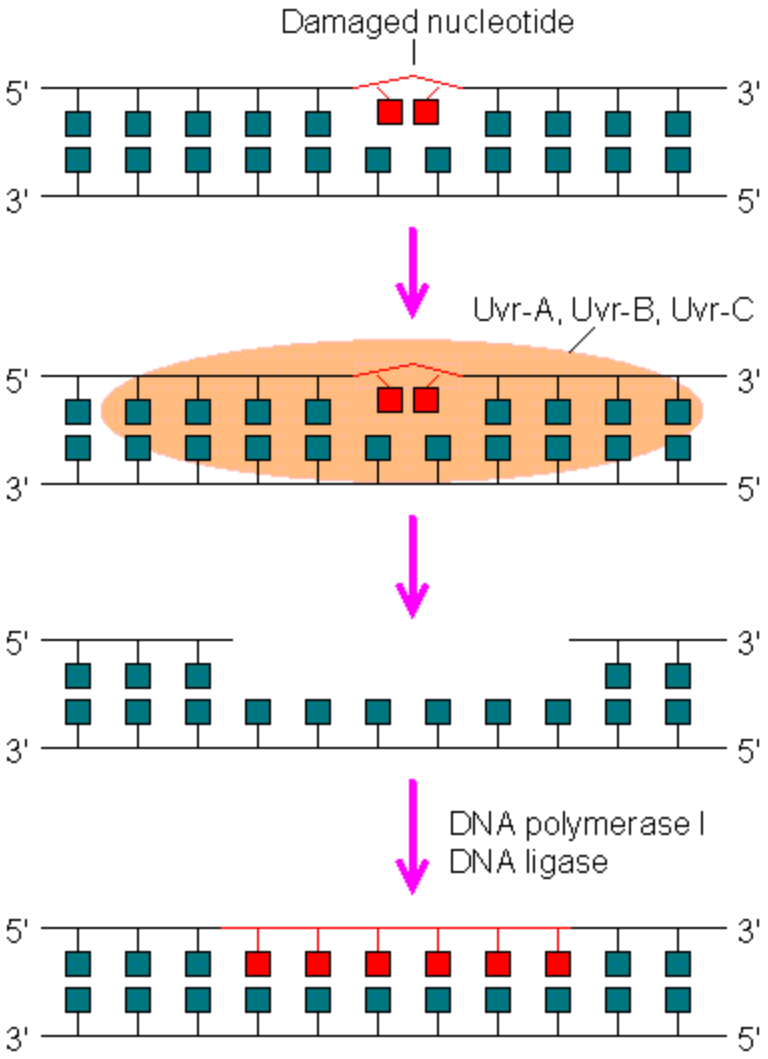
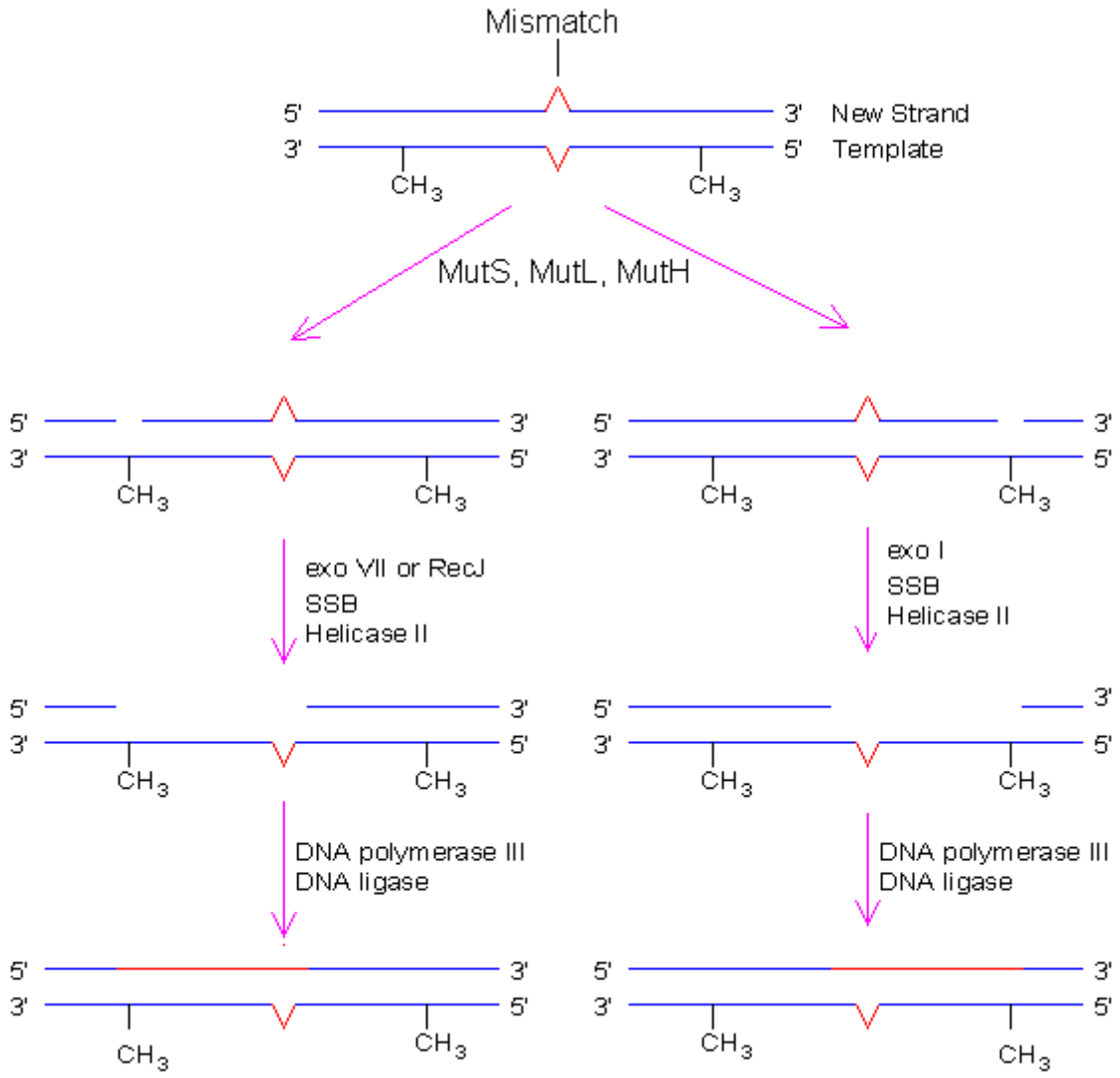
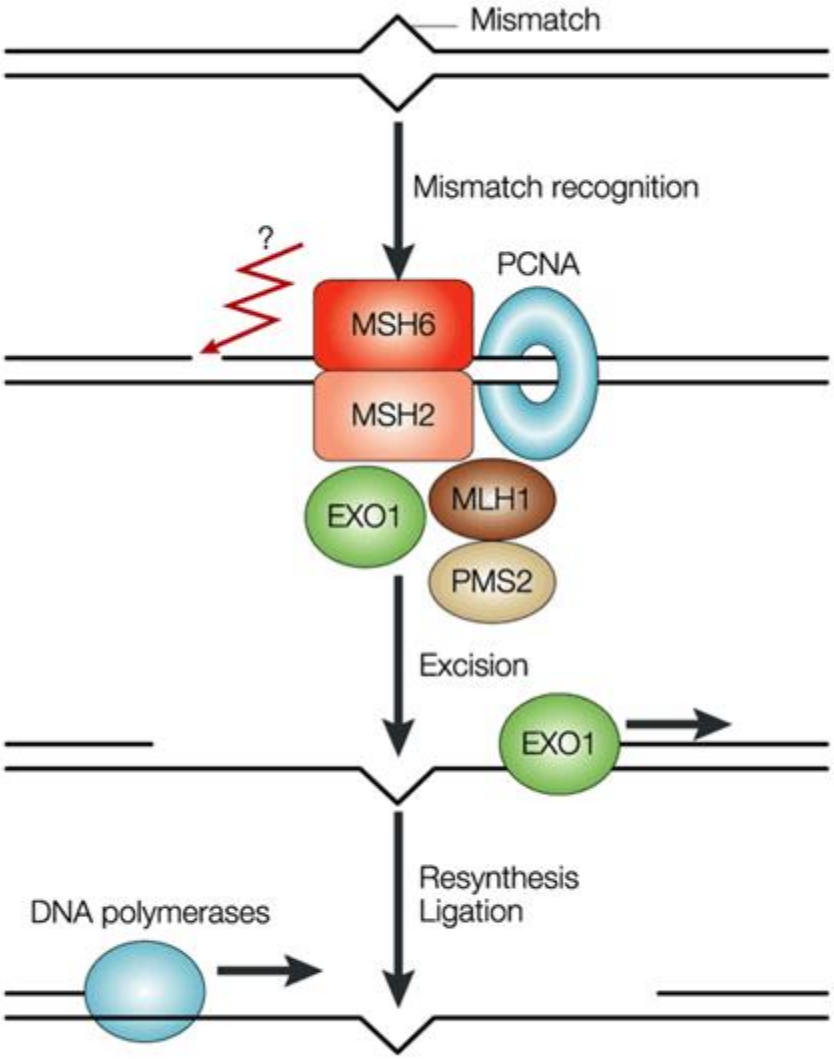
"	MLH3	MLH3	MutLγ; Mismatch repair; endonuclease motif
MutH	?	?	?
uvrD	?	?	?
?	Exonuclease I	Exonuclease I	Excision (5' to 3' polarity)
?	RFC, PCNA, Polγ	RFC, PCNA, Polγ	Nick identification; gap filling


Damaged base
5'
3'
3'
5'
DNA glycosylase
AP site
5'
3'
3'
5'
AP endonuclease
5'
3'
3'
5'
DNA polymerase I
DNA ligase
5'
3'
3'
5'


Damaged nucleotide
5'
3'
3'
5'
Uvr-A, Uvr-B, Uvr-C
5'
3'
3'
5'
5'
3'
3'
5'
DNA polymerase I
DNA ligase
5'
3'
3'
5'


Mismatch
5'
3'
New Strand
3'
5'
Template
CH3
CH3
MutS, MutL, MutH
exo VII or RecJ
SSB
Helicase II
exo I
SSB
Helicase II
DNA polymerase III
DNA ligase
DNA polymerase III
DNA ligase



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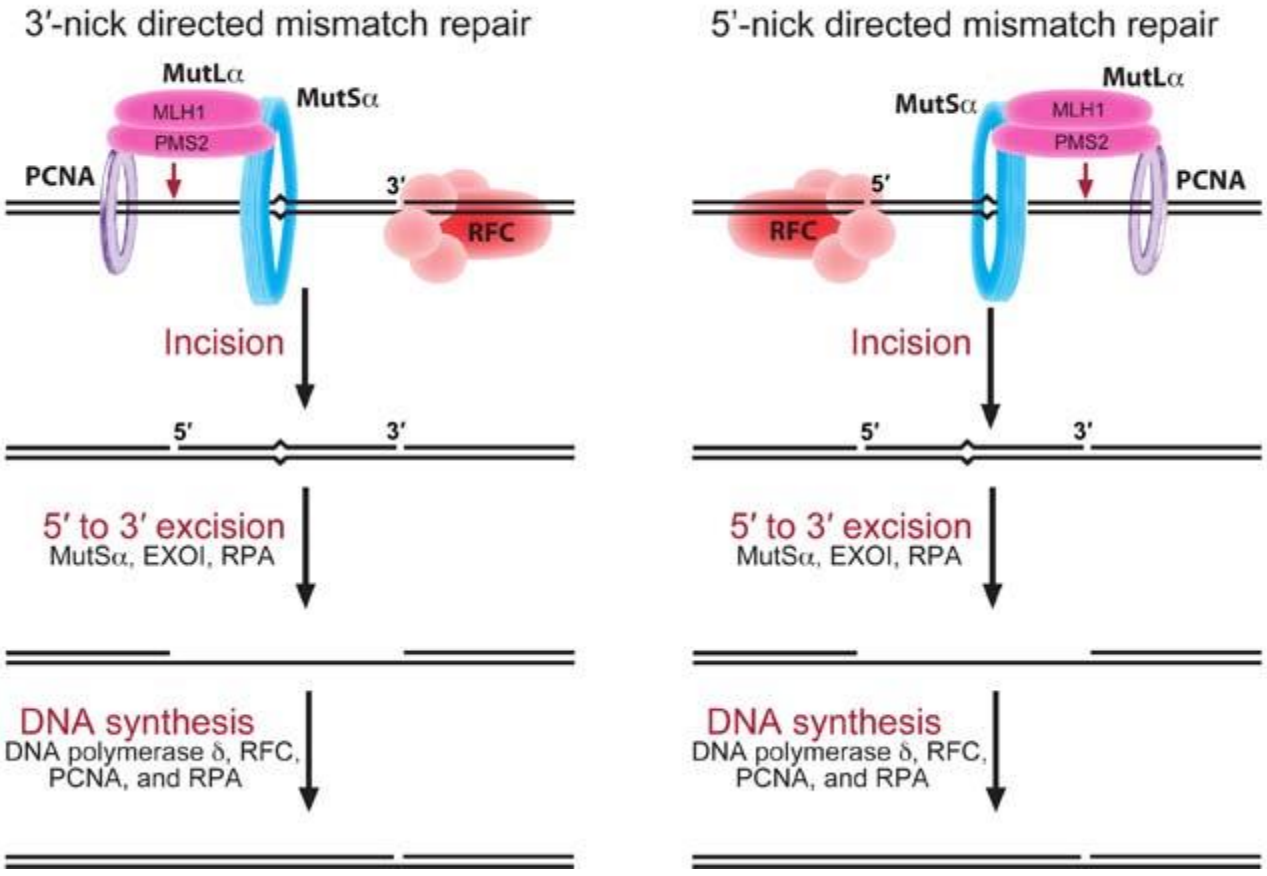
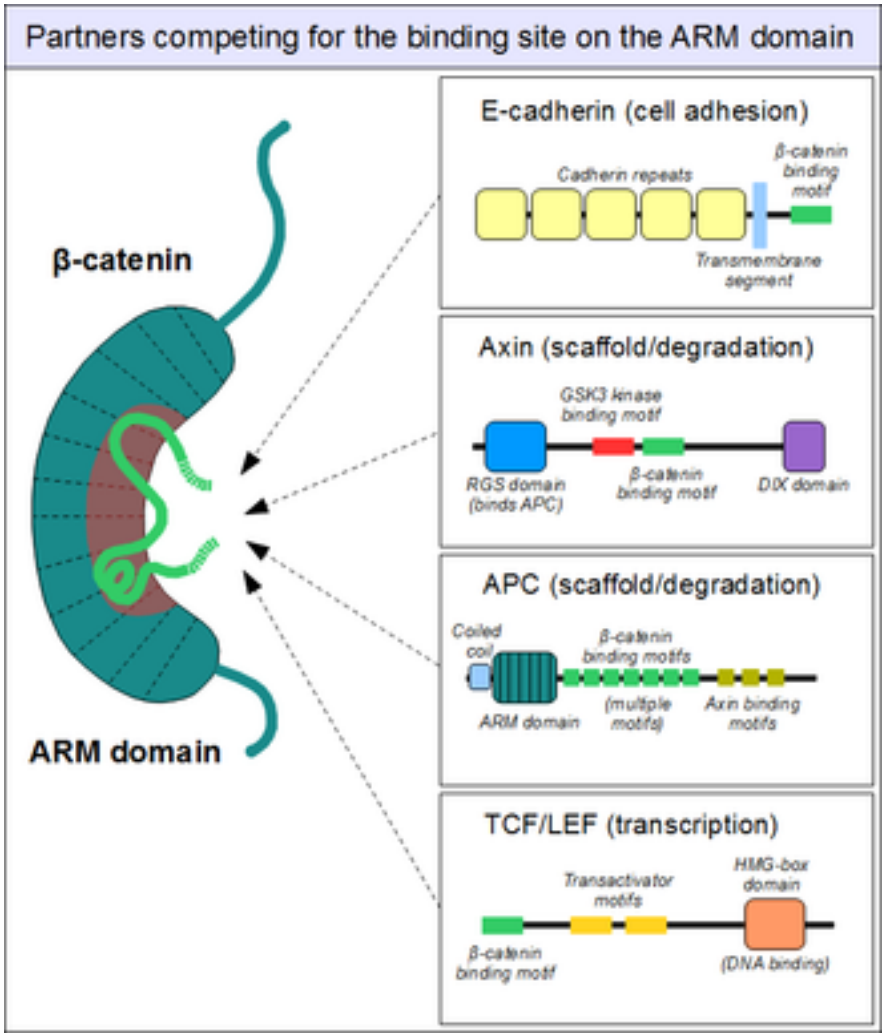
Human mismatch repair




Partners competing for the binding site on the ARM domain
β-catenin
ARM domain
E-cadherin (cell adhesion)
Cadherin repeats
β-catenin binding motif
Transmembrane segment
Axin (scaffold/degradation)
GSK3 kinase binding motif
RGS domain (binds APC)
β-catenin binding motif
DIX domain
APC (scaffold/degradation)
Coiled coil
β-catenin binding motifs
ARM domain
(multiple motifs)
Axin binding motifs
TCF/LEF (transcription)
Transactivator motifs
HMG-box domain
β-catenin binding motif
(DNA binding)

Predisposing Causes

Animal fat intake to be correlated with small-bowel cancer

Consumption of red meat and salt-cured or smoked foods raised the risk of small-bowel cancer 2-3 times.]

Tobacco and alcohol: Predisposing medical conditions

Crohn disease: The relative risk of small-bowel adenocarcinoma is estimated to be between 15 and more than 100 in patients with Crohn disease. Crohn-related tumors generally occur in the ileum, begin until at least 10 years after the onset of Crohn disease, typically occurs more than 20 years afterwards.

Celiac disease (nontropical sprue): A 2001 survey of adult celiac disease found a relative risk of 300 for the development of lymphoma and 67 for the development of adenocarcinoma. Increased incidence of defective DNA mismatch repair compared with those not associated with celiac disease and are also associated with an earlier stage at diagnosis and a better prognosis.

Cancer Lett. 1977 Jul. 3(1-2):83-6.

Cancer Causes Control. 1993 Mar. 4(2):163-9.

. *Cancer Epidemiol Biomarkers Prev*. 1994 Apr-May. 3(3):205-7

Cancer Epidemiol. 2015 Jun. 39 (3): 265-73. .

Cancer Res. 2004 Oct 1. 64(19):7073-7.