大腸直腸癌防治介紹

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臺灣地區主要癌症死亡率趨勢圖

每十萬人口
死亡數

標準化每十萬
人口死亡數

肝癌
肺癌
腸癌

口腔癌(含口腔及下咽)

73 74 75 76 77 78 79 80 81 82 83 84 85 86 87 88 89 90 91 92 93

注：標準化死亡率係以民國七十年臺灣地區男性年中人口
年齡結構為基準。
台灣男女性10大癌症發生分率, 民國95年

(7,167人)肝 17%
(5,793人)結腸及直腸 14%
(5,756人)肺 14%
(4,879人)口腔 12%
(3,073人)攝護腺 7%
(2,455人)胃 6%
(1,624人)食道 4%
(1,406人)膀胱 3%
(1,328人)皮膚 3%
(1,116人)鼻咽 3%
(7,420人)其他癌症 17%

22% 乳房 (6,895人)
14% 結腸及直腸 (4,455人)
9% 肝 (2,925人)
10% 肺 (2,992人)
6% 子宮頸 (1,828人)
4% 胃 (1,339人)
4% 甲狀腺 (1,257人)
4% 子宮體 (1,159人)
4% 皮膚 (1,129人)
3% 卵巢 (1,000人)
20% 其他癌症 (6,297人)

男性共 42,017人
女性共 31,276人

注: 口腔癌含下咽及口咽
General consideration

• Originate from epithelium
• Anatomy: Rectosigmoid
• Colorectal malignancy
  Adenocarcinoma 95%
  Carcinoid
  GISTs
  Lymphoma
Epidemiology

- Second leading cause of cancer death in America and England, third in Taiwan
- Prevalence: 20/100,000
- Gender: male > female in rectal cancer, equal in colon cancer
- Etiology: Genetics and Environmental
  1. First degree relative
  2. HNPCC/FAP
  3. Diet
RISK FACTORS

1. Family history
2. Familial adenomatous polyposis; FAP/HNPCC
3. History of CRC
4. History of colorectal polyps
5. Age
6. Inflammatory bowel disease; IBD
7. Diet
8. Exercise
9. Hormone
10. Others
Natural course of untreated FAP patients

- Age of appearance of adenomas  25 y/o
- Age of onset of symptoms  33 y/o
- Age of diagnosis of adenomas  36 y/o
- Age of diagnosis of carcinoma  39 y/o
- Age of death from carcinoma  42 y/o
Amsterdam criteria for HNPCC

- At least three relatives with histologically verified colorectal cancer, one of which is a first-degree relative of another
- Involvement of at least two generations
- At least one colorectal cancer diagnosed before the age of 50 years
Pathogenesis

Multifactorial

Fearon ER and Vogelstein B 1990

* Mutational activation is initiated by oncogenes (c-myc, ras----etc)

* Mutational inactivation of multiple suppressor genes (p53, DCC, MCC---etc)

* Normal epithelium $\rightarrow$ Epithelial transposition $\rightarrow$ Polyp(Adenoma) $\rightarrow$ Carcinoma in situ $\rightarrow$ Invasive cancer
Symptomatology

1. Bowel habit change
2. Rectal bleeding
3. Tenesmus
4. Mucoid diarrhea
5. Small caliber stool
6. Abdominal pain and abdominal mass
7. Anemia
8. Poor appetite and body weight loss
Diagnosis

1. Rectal digital examination
2. Rigid proctoscopy
3. Flexible sigmoidoscopy
4. Colonoscopy
5. Barium enema examination
6. Tumor marker (CEA)
7. Sonography, CT scan, MRI
Role of CEA

1. Useful for early diagnosis?
2. Useful for prognosis?
3. Useful to detect recurrence?
4. Can second-look operation be based on CEA?
5. Useful to follow treatment response?
6. Non-malignant condition?
Useful for early diagnosis?

No. Few patients (5%) with localized disease have elevated levels
Useful for prognosis?

Yes. Higher levels have poorer prognosis.
Useful to detect recurrence?

Yes. 67-79% of patients have elevated serum levels prior to or at the time of recurrence.
Useful to follow treatment response?

Yes. In 90% of patients, serum CEA levels accurately reflect disease progression or regression.
Staging of colorectal cancer

1. Dukes classification
2. Astler-Coller classification
3. TNM system
4. AJCC/UICC system
DIAGRAM TO SHOW THE VARIOUS LAYERS OF THE WALL OF THE LARGE INTESTINE
THE LARGE INTESTINE

- The caecum
- The appendix
- The ascending colon
- The hepatic flexure
- The transverse colon
- The splenic flexure
- The descending colon
- The rectosigmoid junction
- The sigmoid colon
- The rectum
- The anus
Most colorectal malignancies arise in the membrane lining the bowel wall. As this is glandular tissue the majority of tumours are:

- **ADENOCARCINOMAS**
  - Mucin secreting >80%
  - Mucinous 15%
  - Signet ring cell 2%
- **CARCINOIDS (<1%)**
  - Arising from neuroendocrine cells
- **MALIGNANT LYMPHOMA (<1%)**
  - Tumours may also arise in the muscle wall of the intestine. They may be described as:
    - **Gastrointestinal stromal tumours (GIST)**, which may be of uncertain malignancy (borderline), or invasive.
    - **Leiomyosarcoma**, a malignant tumour of smooth muscle.
PROGNOSTIC FACTORS FOR COLORECTAL CANCER

DUKES STAGE is the most widely accepted and used staging system for colorectal cancer. It was originally introduced as a pathological grade (i.e. taken from the surgical specimen).

- **DUKES STAGE A** Tumour confined to bowel wall
- **DUKES STAGE B** Tumour penetrated bowel wall
- **DUKES STAGE C** Regional lymph nodes involved

- **DUKES STAGE D** has been added more recently to show that metastases are present. *(Not possible to tell this from a colectomy specimen)*

Stage B may be divided according to whether the tumour has just penetrated the outer surface of the bowel wall (B1) or the surrounding tissues are involved (B2), and stage C according to whether the apical nodes are involved (C2) or not (C1).

The ASTLER-COLLER system is based on Dukes but the values: A, B1, B2, C1, C2, D1, D2 have slightly different definitions.
DUKES CLASSIFICATION OF COLORECTAL TUMOURS

Diagram

Regional lymph nodes

Dukes C tumour involving regional nodes

Dukes B tumour invading pericolic/perirectal tissue

Dukes A tumour confined to bowel wall

Bowel wall

(Direct extension)

(localised)
THE CANCER REGISTRY STAGING SYSTEM

Cancer registries use a simplified staging system for all tumour sites which indicates how far a tumour has spread at diagnosis:

• **LOCALISED** - confined to the organ of origin.

• **DIRECT EXTENSION** - spread to tissue next to the organ of origin.

• **REGIONAL LYMPH NODE INVOLVEMENT** – lymph nodes nearest to the organ of origin involved.

• **DISTANT METASTASES** present – tumour cells have been carried to another part of the body via the blood stream, or to distant lymph nodes.

*Duke’s B can be divided between B1, where the tumour has not penetrated beyond the bowel wall – localised disease, and B2 where it has – direct extension.*
OTHER PROGNOSTIC FACTORS FOR COLORECTAL CANCER

Other, more sophisticated staging and grading systems have been introduced, e.g. JASS, which deals with a number of different prognostic factors, but DUKES is the most important being the most widely accepted and used.

- Classical STAGE is derived from UICC TNM has the following values:
  stages 0, 1, 2A, 2B, 3A, 3B, 3C, 4

N.B. Cancer registries record how far the patient’s tumour has spread (i.e. the tumour stage) AT DIAGNOSIS.
TNM cancer classification system

Primary tumor (T)
Tx Primary tumor cannot be assessed
T0 No evidence of primary tumor
Tis Carcinoma in situ
T1 Tumor invades submucosa
T2 Tumor invades muscularis propria
T3 Tumor invades through the muscularis propria into the subserosa or into nonperitonealized pericolic or perirectal tissue
T4 Tumor perforates the visceral peritoneum or directly invades other organs or structures
TNM cancer classification system

Regional lymph node (N)
Nx Regional lymph nodes cannot be assessed
N0 No regional lymph nodes metastasis
N1 Metastasis to 1 to 3 pericolic or perirectal lymph nodes
N2 Metastasis to 4 or more pericolic or perirectal lymph nodes
N3 Metastasis to any lymph nodes along the course of a named vascular trunk
TNM cancer classification system

Distant metastases (M)
Mx Presence of distant metastasis cannot be assessed
M0 No distant metastasis
M1 Distant metastasis
The stage of the TNM system

Stage I : T1 or T2, N0, M0
Stage II : T3 or T4, N0, M0
Stage III: Any T, N1-N3, M0
Stage IV: Any T, Any N, M1
Treatment

Depends on preoperative evaluation and clinical presentations

1. Surgical treatment
2. Systemic chemotherapy
3. Radiation therapy
Complication of colorectal cancer

- Obstruction
- Perforation
- Bleeding
- Septicemia
Obstruction

- Carcinoma is the most common cause of large bowel obstruction, contributing to 60% of cases in the elderly
- Left colon
- Incidences range from 7% to 29%
- A nonspecific type of colitis may develop proximal to an obstructing carcinoma of the colon
- Diminished survival
Perforation

• Incidence is in the 6% to 12% range
• In conjunction with obstruction in about 1% of patients with colorectal carcinoma
• Site of perforation: carcinoma itself or cecum
Bleeding

- Bleeding is a very common symptom of colorectal carcinoma, but massive bleeding is an uncommon presentation.
Septicemia

• With or without endocarditis, septicemia caused by Streptococcus bovis may be associated with an occult colonic malignancy

• All patients with endocarditis caused by S. bovis should be evaluated for concomitant colon cancer
Treatment Strategies
It's not just about chemotherapy

SCREENING: prevention better than cure

SURGERY: TME & rectal cancer; Liver resection

RADIOThERAPY: improvements in rectal cancer

CYTOTOXIC CHEMOTHERAPY: what to give, when and to whom

NOVEL AGENTS: a new horizon but can we afford it

TO BOLDLY GO
FOBT Screening

化學法(gFOBT)來偵測大便潛血 紅血球內含的酵素可以催化過氧化氫，進而產生氧化及顏色變化。Guaiac零陵香木試驗可偵測任何的血色素，包括動物血、藥物及某些水果蔬菜，因含有過氧化酶，因此會得到假陽性。

免疫化學方法(iFOBT)來偵測血紅蛋白，它只對人類血紅素、球蛋白、及一些早期的分解物有反應，理論上應可達到較高的特異性。
Terminology

* Monotherapy: oral, IV(bolus or infusional)
* Combination therapy
  1) Doublet: Folfox, Folfiri, Xelox, Xeliri
  2) Triplet: Folfoxiriri
  3) Target therapy: Avastin+C/T or Erbitux+C/T
* Metronomic, Adjuvant, Neoadjuvant, Palliative, CCRT(concurrent chemoradiotherapy) etc.
First line chemotherapy in CRC: the evolution of benefit

- **Response Rate (%)**
- **Median Survival (months)**

- BSC
- bolus 5FU
- 5-FU/FA Mayo
- 5-FU/FA infusional
- 5-FU/LOHP
- 5-FU/lirinotecan

**Legend:**
- Orange: Response Rate (%)
- Turquoise: Median Survival (months)
CRC treatment landscape

- 1950: 5-FU
- 1960: Addition of LV to 5-FU
- 1970: Irinotecan
- 1980: Oxaliplatin
- 1990: Avastin
- 2000: Panitumumab
- 2010: Cetuximab, Xeloda
Active Cytotoxics in Colorectal Cancer

5 - Fluorouracil

Irinotecan

Capecitabine

Oxaliplatin
Oxaliplatin is a water soluble platinum derivative with an oxalate ligand and a 1, 2-diaminocyclohexane (DACH) carrier ligand. The structure of Oxaliplatin is shown in the diagram. cisplatin, on the other hand, is a different type of platinum compound with a different structure.

trans-1-dach (1R, 2R-dach) oxalatoplatinum
Platinum Cytotoxicity

- Formation of platinated inter- and intrastrand adducts, leading to inhibition of DNA synthesis

. Cvitkovic, BJC 1998; 77 (suppl.4): 8-11
FOLFOX4: LV5FU2 + Oxaliplatin 85 mg/m2

Every 2 weeks, 6 months treatment (12 cy)

*Baxter LV5 infusors
Neurotoxicity Grading

Gr 1. P/D that do not interfere with function

Gr 2. P/D interfering with function, but not ADL

Gr. 3 P/D with pain or interference with ADL

Gr. 4 Persistent PD that are disabling or life-threatening
Ca\textsuperscript{2+} / Mg\textsuperscript{2+}

161 patients

5FU+ Oxaliplatin
oxaliplatin
(85/2w, 100/2w, 130/3w)

Ca gluconate / Mg sulfate

Observation

Ca gluconate 1 g / Mg chloride 1 g

i.v. 15min

Oxaliplatin

Ca gluconate 1 g / Mg chloride 1 g

i.v. 15min

5-FU + LV

Laurence Gamelin, Clin Can Res; 2004
CAMPTO® (irinotecan HCl)
Prescription Information
Irinotecan - Pharmacokinetics

- Irinotecan has a mean terminal elimination half-life of 6 to 12 hours
  - The mean terminal elimination half-life of the active metabolite SN-38 is 10 to 20 hours
- Over the recommended dose range (50 to 350 mg/m$^2$) the AUC of irinotecan increases linearly with dose
- Maximum concentrations of the active metabolite SN-38 are generally seen within 1 hour following a 90-minute infusion
Recommended Dosage and Administration

- In combination therapy with 5FU and FA (Folfiri regimen):
  - 150 - 180 mg/m² administered once every 2 weeks as an intravenous infusion over a 90-minute period, followed by infusion with FA and 5-FU.
Important Considerations

- Both early and late forms of diarrhea can occur:
  - Late diarrhea should be managed promptly with loperamide and supportive care including antibiotics as needed.
- Use of a colony-stimulating factor may be considered in patients with significant neutropenia.
Oral Fluoropyrimidines

Strategies;

Prodrug activation within tumour cells: CAPECITABINE

Inhibition of 5FU metabolising enzymes to improve bioavailability

UFT (tegafur:uracil – 1:4);
S1 (tegafur, CDHP, oxonic acid)
Oral 5-FU in Adj Study: NSABP C-06 and X-ACT

<table>
<thead>
<tr>
<th>Efficacy</th>
<th>UFT</th>
<th>5-FU</th>
<th>P value</th>
<th>Xeloda</th>
<th>5-FU</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr DFS</td>
<td>74.5%</td>
<td>74.5%</td>
<td>NS</td>
<td>64.2%</td>
<td>60.6%</td>
<td>P=0.0528</td>
</tr>
<tr>
<td>3-yr RFS</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>65.5%</td>
<td>61.9%</td>
<td>P=0.0407</td>
</tr>
<tr>
<td>3-yr OS</td>
<td>85%</td>
<td>84%</td>
<td>NS</td>
<td>81.3%</td>
<td>77.6%</td>
<td>P=0.0706</td>
</tr>
</tbody>
</table>

NS= Not significant

### Oral 5-FU in Adj Study: NSABP C06 and X-ACT

<table>
<thead>
<tr>
<th>G3/4 Toxicity</th>
<th>UFT</th>
<th>5-FU</th>
<th>Xeloda</th>
<th>5-FU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Granulocytopenia</td>
<td>1%</td>
<td>1%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>29%</td>
<td>28%</td>
<td>12%</td>
<td>14%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1%</td>
<td>1%</td>
<td>1%</td>
<td>8%</td>
</tr>
<tr>
<td>HFS</td>
<td>0%</td>
<td>0%</td>
<td>18%</td>
<td>1%</td>
</tr>
<tr>
<td>N&amp;V</td>
<td>&lt;4%</td>
<td>3%</td>
<td>4%</td>
<td>3%</td>
</tr>
</tbody>
</table>

## Safety of Tegafur/Uracil

### Summary of Adverse Events with Tegafur/Uracil and 5-FU

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Tegadur/Uracil (n=21,762) 300-600mg/d</th>
<th>5FU bolus (n=88) 500mg/m2/d x 5 q5w</th>
<th>SWOG : 8904 5FU CI (n=85) 300mg/m2/d d1-28 q5w</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>No.</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>390</td>
<td>1.8</td>
<td>43</td>
</tr>
<tr>
<td>Anorexia</td>
<td>957</td>
<td>4.4</td>
<td>NR</td>
</tr>
<tr>
<td>Nausea</td>
<td>597</td>
<td>2.7</td>
<td>NR</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>119</td>
<td>0.6</td>
<td>44</td>
</tr>
<tr>
<td>Vomiting</td>
<td>301</td>
<td>1.4</td>
<td>27</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>723</td>
<td>3.3</td>
<td>58</td>
</tr>
<tr>
<td>Granulocytopenia</td>
<td>29</td>
<td>0.1</td>
<td>58</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>240</td>
<td>1.1</td>
<td>23</td>
</tr>
</tbody>
</table>

Adverse Event Safety of Tegafur/Uracil

Summary of Adverse Events with Tegafur/Uracil and 5-FU

J Clin Oncol 1998, 16:2877-85
手足症候群

(Hand-Foot Syndrome)

手足症候群為最常見的 Xeloda 的副作用，特徵如下：

- 手、足部發紅，局部麻木感或感覺異常為第一級手足症候群。

- 出現疼痛性紅斑及手部、足部腫大，或影響到病患每日活動之不適感則定義為第二級。
第三級手足症候群的定義為湿性脫屑、潰爛、起水泡及手或足部之嚴重疼痛，或造成病患無法工作或從事日常活動的嚴重不適感。

當發生第二級手足症候群時一定要先停藥，並請求醫師協助，直到恢復第一級或是完全正常，才可重新服藥。如果這時候不先停藥，症狀一定會更嚴重，便成第三級的手足症候群。

圖 3：一種第三級手足症候群
# 藥物健保給付規範

<table>
<thead>
<tr>
<th></th>
<th>UFUR/UFT</th>
<th>Xeloda</th>
</tr>
</thead>
<tbody>
<tr>
<td>主成分</td>
<td>Tegafur-Uracil</td>
<td>Capecitanine</td>
</tr>
<tr>
<td>T1/2</td>
<td>7~13hr</td>
<td>45 minutes</td>
</tr>
<tr>
<td>Contraindication</td>
<td>Sorivudine, Phenytoin</td>
<td>Sorivudine, Phenytoin, Coumarin</td>
</tr>
<tr>
<td>健保給付價格</td>
<td>77/71</td>
<td>131</td>
</tr>
</tbody>
</table>
| 健保給付規範 | **3.大腸癌、結腸癌第Ⅱ、Ⅲ期患者之術後輔助性治療，且使用期限不得超過2年(94/10/1)** | **3.Xeloda可作為治療轉移性結腸直腸癌的第一線用藥**  
**4.第三期結腸癌患者手術後的輔助性療法，以八個療程為限 (96/9/1)** |
XELOX Phase I study: recommended regimen in mCRC

- **oxaliplatin**
  - 130mg/m² (2-hour infusion) d1

- Xeloda
  - 1000mg/m² d1–14 bid q3w

**Grade 3/4 AEs:**
- diarrhoea (26%), thrombocytopenia (22%), neutropenia (17%), paraesthesia (13%)

**ORR:** 26%, response duration: 4.9 months

Targeted Therapies

**EGFR**

Overexpression associated with poor prognosis in colorectal cancer

Strategies:
- MAb binding to & inactivation of receptor
- Small molecule inhibition of active TK site

**ANGIOGENESIS**

Microvessel density & VEGF expression correlate with worse prognosis in colorectal cancer.

Strategies:
- MAb innactivators of ligands & receptors
- Small molecule TKI
“Targeted” Therapy: Examples

Growth Factor Inhibitors:

• Anti-EGFR (Epidermal Growth Factor Receptor)

• Anti-VEGF (Vascular Endothelial Growth Factor)
CETUXIMAB
Chimeric IgG1 Mab for EGFR

Phase II study data

BOND study:

≥1 prior regime (Ir/5FU) EGFR +ve

Cetuximab (n=111)

OR – 10.8%
mTTP = 1.5 month

Cetuximab + Irinotecan (n=218)

OR – 22.9%
mTTP = 4.1 month
EGF receptor signaling pathway: A rationale for personalized therapy

Ligand: AREG/EREG
Target for EGFR-ERBITUX

Target for EGFT-TK inhibitor

PTEN

P13K

pY

pY

Grb2

Sos

Ras

Raf

Mek

Mapk

Ptten

Akt

Stat

Gene transcription
Cell-cycle progression

Myc

Jun

fos

Gene transcription
Cell-cycle progression

Myc

Cyclin D1

Chemotherapy/
radiotherapy resistance

Invasion and metastasis

Angiogenesis

Survival (anti-apoptosis)

Proliferation/
maturation

KRAS mutations: Occur in 40% of colorectal cancer tumors – an early event

Targeting the EGFR pathway: 

**K-Ras mutations**

- **EGFR overexpression:**
  - CRC (27–77%)
  - Pancreatic cancer (30–50%)
  - Lung cancer (40–80%)
  - NSCLC (14–91%)

- **Ras mutation:**
  - CRC (50%)
  - Pancreatic cancer (90%)
  - Papillary thyroid cancer (60%)
  - NSCLC (30%)

- **B-Raf mutation:**
  - CRC (10%)
  - Melanoma (70%)
  - Papillary thyroid cancer (50%)

Adapted from Roberts Der. Oncogene 2007
ERBITUX® (cetuximab)
Safety and tolerability
ERBITUX safety and tolerability (1)

- ERBITUX is generally well tolerated as monotherapy and in combination with irinotecan-, oxaliplatin- and platinum-based chemotherapy.

- ERBITUX does not increase the toxicity of cytotoxic chemotherapy or radiotherapy.

- The most common adverse events related to ERBITUX are skin reactions, particularly an acne-like rash, which may develop in approx. 80% of patients. 85% of these reactions are mild-to-moderate.

- There is a strong correlation between development of acne-like rash and response to treatment.
Other adverse events observed with ERBITUX include:

- Nail disorders, e.g. paronychia
- Eye disorders
- Respiratory disorders
- Infusion-related reactions (IRRs)
  - mild to moderate reactions occur in more than 10% of patients with severe reactions occurring in 1 - 10% of patients
  - in a post hoc analysis of the MABEL study only 1% of patients treated with antihistamines and corticosteroids as prophylactic medication had grade 3/4 IRRs
EGFR inhibitor-related skin reactions
ERBITUX
Skin reactions

- Skin reactions are a common feature of treatment with many EGFR inhibitors
- Skin reactions are seen in approx. 80% of patients treated with ERBITUX
  - 85% are mild-to-moderate
- Skin reactions typically present as acne-like rash
- Pruritus, dry skin and nail disorders (e.g. paronychia) are observed less frequently
- Skin reactions are generally manageable and should rarely be a reason for discontinuing treatment
ERBITUX
Management of skin reactions

**Acne-like rash**
- **MILD/MODERATE RASH**
  - Clindamycin
  - Erythromycin
  - Benzoyl peroxide
  - Metronidazole
  - Topical retinoids may be used sparingly

**Itching**
- Antihistamines
- Treat dry skin if necessary

**Fissures**
- Topical emollients + salicylic acid
- Hydrocolloid dressing
- Steroid tape
- Topical antibiotic if required

**Paronychia**
- Topical antibiotic creams or soaks

**MODERATE/SEVERE RASH**
- Topical treatment as before, plus systemic treatment
- Second generation tetracyclines (doxycycline, minocycline)
- Treat for at least 12 weeks. Possible adverse effects

Correlation between skin reactions and response to treatment with ERBITUX

- The presence and/or intensity of skin reactions correlates strongly with response to ERBITUX and survival.

- This relationship has been observed in different tumor types, including CRC and SCCHN.

- However, patients not developing skin reactions may also respond to treatment with ERBITUX.
**Anti-angiogenic agents**

**Bevacizumab**

Humanized anti VEGF monoclonal antibody

Inhibits angiogenesis

Registration trial; Phase III

1st line advanced colorectal cancer

<table>
<thead>
<tr>
<th></th>
<th>IFL/placebo (n=412)</th>
<th>IFL/bevacizumab (n=403)</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>35%</td>
<td>45%</td>
</tr>
<tr>
<td>mTTP</td>
<td>6.2</td>
<td>10.6</td>
</tr>
<tr>
<td>mOS</td>
<td>15.6</td>
<td>20.3</td>
</tr>
</tbody>
</table>

Toxicity - hypertension / perforation
Avastin™
Bevacizumab
100 mg/4 ml
1 vial of 4 ml of concentrate for solution for infusion
Roche
什麼是VEGF？

VEGF 全名是vascular endothelial growth factor，中文是血管內皮生長因子，是腫瘤細胞分泌促使血管新生的重要因子。當VEGF和它位於血管內皮細胞上的接受器結合，會促使新血管的生成，幫助腫瘤細胞生長。
Agents targeting the VEGF pathway

**Agents** targeting the VEGF pathway include:

- **Agents inhibiting VEGF receptors**
  - Antibodies inhibiting VEGF (e.g. Avastin™)
  - Small-molecules inhibiting VEGF receptors (TKIs) (e.g. PTK-787)
- **Ribozymes** (Angiozyme)
- **Soluble VEGF receptors** (VEGF-TRAP)

**Pathways** affected:

- Migration, permeability, DNA synthesis, survival
- Angiogenesis
- Lymphangiogenesis

**Notes:**

- Cation channel
- Permeability
什麼是癌思停(Avastin)？

癌思停(Avastin)是第一個抑制血管新生(anti-angiogenesis)的單株抗體(monoclonal antibody)，可以和血管內皮生長因子(vascular endothelial growth factor, VEGF)結合，藉由抑制血管的新生，而抑制癌細胞的生長。
使用癌思停(Avastin)有哪些需要特別注意的事項？

胃腸穿孔：轉移性大腸或直腸癌患者在使用癌思停(Avastin)及化學療法時，會有發生胃腸穿孔的危險，發生的機率約1.5%。

高血壓：以癌思停(Avastin)治療之患者的高血壓發生率較高。建議在治療期間，每二個星期定期監測患者的血壓。如果高血壓無法以藥物治療控制，應永久停用癌思停(Avastin)的治療。

傷口癒合：重大手術後至少28天或手術傷口完全癒合後，再開始進行癌思停(Avastin)的治療。
使用癌思停(Avastin)有哪些需要特别注意的事項？

🏆 動脈血栓栓塞：有動脈血栓栓塞病史或年齡超過65歲的患者，在癌思停(Avastin)治療期間發生動脈血栓栓塞的危險性會增加。

🏆 出血：在癌思停(Avastin)治療期間出現3級或4級出血的患者應永久停用癌思停(Avastin)。
癌思停(Avastin)—注射劑—儲存2~8℃

常识

100mg / 4 ml : 17750元
Q2w : 5 mg / kg ; Q3w : 7.5 mg / kg
稀釋至100 c.c 0.9%生理食鹽水調配時不可以用力搖晃。
第一次90分鐘在化學治療之後
若耐受性良好第二次60 分鐘在化學治療之前或後
若耐受性良好第三次以後30 分鐘在化學治療之前或後
稀釋後在室溫可保持12小時安定 ； 在2~8℃可保持24小時安定
Avastin (bevacizumab) 與含有irinotecan/5-fluorouracil/leucovorin 或5-fluorouracil/leucovorin 的化學療法合併使用，可以作為轉移性大腸或直腸癌患者的第一線治療。

Avastin 與含有5-fluorouracil/leucovorin/oxaliplatin 的化學療法合併使用，可以作為先前接受過以fluoropyrimidine 為基礎的化學療法無效且未曾接受過Avastin 治療的轉移性大腸或直腸癌患者的治療。
The pharmacogenomic revolution

Genetic polymorphisms & drug metabolism / effect

Prognostic & Predictive markers

Individualisation of treatment

5FU
TS
DPD

Oxaliplatin
ERCC2
XRCC1
GSTP1

Irinotecan
UGT1A1