In the early stages of CRC, the disease may be cured with surgery alone. However, symptoms of CRC are often vague and, despite it being one of the most common cancers worldwide,1 public awareness of the disease is low.2 One in four patients is diagnosed when the cancer has already spread (metastasized), via the bloodstream and lymph nodes in the colon, to other organs in the body.3 This advanced stage of the disease, which is known as metastatic CRC (mCRC), is difficult to treat and is associated with low survival rates.4

Useful statistics

- Worldwide, in terms of incidence, CRC is the third most commonly occurring cancer in men (after lung and prostate cancer) and the second in women (after breast cancer):1
  - Worldwide approximately 1.36 million new cases of CRC are estimated to occur every year, accounting for 9.7% of all cancers1
  - CRC accounts for 10.0% (746,000) of all new cancers in men and about 9.2% (614,000) of new cancers in women worldwide1
  - Almost 55% of CRC cases are diagnosed in developed regions of the world, CRC diagnosis rates are highest in Australia and New Zealand, with the lowest rates found in Western Africa1
  - A quarter of CRC patients present with metastatic disease (mCRC).3
  - In terms of prevalence, CRC is the second most common cancer worldwide, after breast cancer.5

- CRC is the most commonly occurring cancer in Europe, with 447,000 new cases in 2012.6 After lung cancer, CRC is the most common cause of cancer-related deaths on the continent.6
- Only 44% of the public can name a symptom of CRC.2
- Overall mortality caused by CRC varies according to local screening practices and the stage at which the disease is diagnosed:
  - In Europe, long-term follow-up studies show that around 50% of people diagnosed with CRC eventually die of the disease7
  - Approximately 694,000 people worldwide die from the disease each year, accounting for 8.5% of all cancer deaths and making CRC the fourth most common cause of death from cancer.1
  - In developed countries, patients with mCRC currently have a five-year survival rate of approximately 10–12.5%.5,8

Risk factors9

- Age: More than 90% of people diagnosed with CRC are over 50 years old.
- Medical history: A previous history of CRC, colorectal polyps or chronic inflammatory bowel disease (such as ulcerative colitis or Crohn’s disease).
- Family history: Certain genetic mutations or a family history of CRC and/or polyps.
- Diet: A diet high in red and processed meats.
- Other factors: Physical inactivity, obesity, smoking and high alcohol intake.

Symptoms10

CRC symptoms are non-specific and may include:

- Blood/mucus in the stool
- Changes in bowel habits such as diarrhea or constipation
- Feeling of needing the toilet after having emptied the bowel
- Pain or discomfort
- Unexplained weight loss
- Constant tiredness
- Unexplained iron-deficiency anemia (low number of red blood cells).
Stages

Staging is a way of describing a cancer based on where it is located, if or where it has spread, and if it is affecting the functions of other organs in the body:

- **Stage 0**: Very early cancer on the innermost layer of the colon (‘in situ’)
- **Stage I**: The cancer is in the inner layers of the colon and is surrounded by normal tissue
- **Stage II**: The cancer has spread through the muscle wall of the colon, but has not yet breached it
- **Stage III**: The cancer has spread to nearby lymph nodes
- **Stage IV**: The cancer has spread to other areas within the body (metastasis).

Treatment options

The therapeutic approach used to treat cancer depends on the stage and location of the tumor. Cancers affecting the colon are usually treated in a different way to cancers of the rectum.

Surgery

In the early stages of CRC, surgery is a particularly important treatment option. If the malignant tissue can be entirely removed by surgery it offers the possibility of cure. In advanced or recurrent CRC, surgery is unlikely to cure the disease as cancer cells are likely to have spread to other areas of the body and/or tumors may have become too large to remove safely. Nevertheless, if the metastases have spread only to the liver, complete removal (also called complete resection) of the tumors in the liver along with the primary tumor might offer the potential for the patient to be cured.

In later stages, where metastases have spread beyond the liver, surgery can be used to remove tumors blocking the bowel in order to relieve symptoms. It can also be used to remove remaining metastases from the liver or lungs in order to prolong survival or reduce symptoms.

Adjuvant therapy is administered immediately after surgery to target any residual tumor cells and reduce the risk of recurrence.

Adjuvant therapy may include chemotherapy, radiotherapy and/or a targeted therapy (see below). In advanced disease, these therapies may be administered before surgery (known as neoadjuvant treatment) to improve resection rates.

Radiotherapy

Radiotherapy uses high-energy X-rays or gamma irradiation to kill cancer cells. Radiotherapy is most often used to treat rectal cancer, either before surgery (neoadjuvant setting) to reduce the tumor size, or after surgery (adjuvant setting) to reduce the risk of relapse.

In patients with mCRC, radiotherapy may be combined with chemotherapy (chemoradiotherapy) or used to relieve symptoms (palliative treatment).

Chemotherapy

Chemotherapy can be used both before surgery in order to reduce the size of the tumor, or after surgery to help stop the cancer from coming back (recurrence). In advanced (metastatic) stages, chemotherapy is often used as part of palliative treatment to shrink tumors, alleviate symptoms and discomfort, and prolong survival.

Targeted therapy

In recent years, a number of targeted therapies have been developed for the treatment of mCRC. These innovative therapies target faulty proteins that are present in unusually large amounts in certain CRC cells and that contribute to cancer growth and development.

Monoclonal antibodies are a type of targeted therapy that work by binding to specific proteins on the surface of cancer cells, thereby interfering with the cell's capacity to grow and divide. They can be more effective and tolerable than traditional treatments such as chemotherapy, as they specifically attack cancer cells, leaving most healthy cells unharmed.

Erbitux® (cetuximab) is a type of monoclonal antibody that specifically targets the epidermal growth factor receptor (EGFR) and thereby inhibits cell proliferation, survival, motility, invasion and tumor angiogenesis (blood vessel growth). Erbitux has been demonstrated to be effective in the treatment of mCRC, both as a single agent and in combination with standard chemotherapy regimens.
Personalized therapies: Biomarkers in the treatment of metastatic colorectal cancer\textsuperscript{11–13}

The latest research demonstrates that identification of specific molecules (biomarkers) in certain cancer types can help physicians identify which patients are most likely to benefit from specific treatments. This breakthrough means oncologists are able to select the most appropriate treatment for patients from the point of diagnosis and thus improve their overall long-term outcomes. For example, genes, such as RAS, that code for proteins involved in the EGFR signaling pathway, have been identified as biomarkers in mCRC.

Approximately 50\% of patients with mCRC have tumors with an EGFR signaling pathway containing the ‘normal’ (wild-type) form of RAS proteins, while the remaining patients carry the mutant RAS proteins.\textsuperscript{14} In tumors with mutant RAS genes, the RAS proteins are permanently ‘switched on’, regardless of EGFR-mediated signaling upstream. As a result, the EGFR signaling pathway is largely unresponsive to external factors, for example, Erbitux, that would otherwise be expected to switch it off. Clinical trials have shown that RAS gene status predicts whether a patient may respond to Erbitux treatment and have demonstrated that patients with mCRC with RAS wild-type tumors are most likely to benefit from this therapy.\textsuperscript{15}

Based on these data, the European Commission approved an update to the Erbitux label for the treatment of patients with EGFR-expressing, RAS wild-type mCRC:

- Erbitux is now indicated for the treatment of patients with EGFR-expressing, RAS wild-type mCRC in combination with irinotecan-based chemotherapy, in 1st line in combination with FOLFOX, or as a single agent in patients who have failed oxaliplatin- and irinotecan-based therapy and who are intolerant to irinotecan.

• Erbitux is contraindicated in combination with oxaliplatin-containing chemotherapy for patients with mutant RAS mCRC or for whom RAS mCRC status is unknown.

References


For more information on Erbitux in colorectal and head & neck cancer, please visit: www.globalcancernews.com.