Cancer-Related Abdominal Pain

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Introduction

Among the most frequently occurring cancers worldwide is gastrointestinal cancer, with variable rates depending on region. For instance, the highest prevalence of colorectal cancer is found in countries such as the USA, Japan, and parts of Europe and Australia, whereas liver cancer and stomach cancer are relatively more prevalent in Asia and Africa [1]. It appears that environmental, lifestyle, and inherited factors contribute to tumor etiology.

According to the National Cancer Institute Surveillance Epidemiology and End Results (NCI SEER) incidence data, it is estimated that approximately 1.66 million Americans will be diagnosed with cancer in the year 2013 [2]. Among those, over 315,000 Americans are diagnosed with cancer involving the digestive system (oropharyngeal, esophageal, stomach, pancreatic, hepatobiliary, intestinal, colorectal, and anal cancer). Per SEER November 2012 submission data, the complete prevalence of Americans with digestive-system cancer is approximately 1.55 million.

Pain is common in cancer patients—it is reported by at least 50 % of cancer patients, and there is a positive correlation between pain and disease stage [3–5]. Cancer-related abdominal pain is a consequence both of alteration or disruption in somatic, neuropathic, and visceral structure and function by the malignant process, and of the associated treatment—whether it is chemotherapy, radiation, surgery, or other modalities—for the underlying malignancy. The intent of this chapter is to describe (1) the pertinent neuroanatomy and physiology of abdominal somatic, visceral, and neuropathic pain, (2) the characteristics of cancer-related abdominal pain, and (3) select cancer-related abdominal pain states both in active cancer patients and in cancer survivors.

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Neuroanatomical and Physiological Considerations in Cancer-Related Abdominal Pain

Pain transmission from the abdomen to the central nervous system occurs through both the somatic sensory and visceral afferent pathways [6]. Somatic pain is characterized as sharp and well localized, whereas visceral pain is described more so as dull, vague, and poorly localized. Somatic and visceral pains are carried by thinly myelinated A-delta fibers and unmyelinated C-fibers. Both the abdominal somatic sensory and visceral afferent cell bodies are located in dorsal root ganglia, which project to the spinal cord dorsal horn, synapsing there with second-order neurons. The second-order dorsal horn cells then send ascending projections via, primarily, the spinothalamic tract (in the anterolateral quadrant of the cord) to the thalamus, which then in turn sends projections to the somatosensory cortex and limbic system. Other ascending pathways related to visceral nociception have been identified as well—the spinoreticular tract, dorsal columns, trigeminoparabrachioamygdaloid tract, and spinohypothalamic tract [7].

Somatic Sensory Innervation of the Abdominal Wall

The lower thoracic ventral spinal rami (from T6 to T11) and the subcostal nerves (T12 ventral rami) provide somatic sensory innervation to the anterolateral abdominal wall, including to the skin, subcutaneous tissue, fascia, muscle, and the parietal peritoneum that lines its internal surface. The T6–T11 ventral rami travel in a neurovascular plane between the transversus abdominis muscle and the internal

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oblique muscle, whereas the T12 subcostal nerve enters the abdomen behind the lateral arcuate ligament, crosses the quadratus lumborum muscle, and enters the neurovascular plane by piercing the transversus abdominis muscle.

Abdominal Visceral Innervation

Receptors (such as end-organ-like Pacinian corpuscles) that respond to various stimuli, such as distention (stretch), spasm, ischemia, hypoxia, and inflammation, are found in the serosal, muscular, and mucosal layers of hollow visceral structures, as well as in the mesentery [8–10]. Silent nociceptors are also present, appearing only after *repeated* visceral nociceptive stimulation or irritation/inflammation. The capsule of solid organs contains visceral afferents; however, the parenchymata of solid organs appear not to be innervated by visceral nociceptors.

Visceral-nociceptive input is carried by peripheral fibers from pseudounipolar neurons, whose cell bodies are located in dorsal root ganglia. These first-order neurons have central projections that travel to the spinal cord, primarily to the marginal zone (lamina I) and substantia gelatinosa (lamina II), among other Rexed laminae (to also include laminae X surrounding the central canal) of the dorsal horn.

Visceral-nociceptive afferent fibers share the same pathways as do the autonomic nervous system fibers (both sympathetic and parasympathetic divisions) to reach the central nervous system. For example, the thoracic splanchnic nerves—which include the greater (from T5 to T9), lesser (from T10 to T11), and least (from T12) thoracic splanchnic nerves (with their cell bodies originating in the thoracic intermediolateral cell column)—are paired nerves that carry preganglionic sympathetic efferent fibers to synapse at prevertebral ganglia, specifically at the celiac plexus, which then in turn sends postganglionic sympathetic fibers to abdominal viscera—to the distal esophagus, stomach, liver, pancreas, biliary tract, gallbladder, kidney, adrenal glands, spleen, omentum, small intestines, and colon (to the splenic flexure distally). The thoracic splanchnic nerves and celiac plexus, however, *also* relay visceral *afferent* fibers from these abdominal viscera, back to the central nervous system, synapsing at the spinal dorsal horn.

The celiac plexus is the largest of the three prevertebral sympathetic plexuses (the other two, for completeness, being the cardiac plexus and the hypogastric plexuses). It is a retroperitoneal structure composed of 1–5 ganglia, and it is found anterolateral to the aorta (in close proximity to the origin of the celiac artery) at the level of the T12 or L1 vertebra (Fig. 13.1). Both the celiac plexus and thoracic splanchnic nerves serve as targets in interventional pain medicine for visceral analgesia in intra-abdominal cancer pain states.

Distal to the splenic flexure of the large intestine, the visceral-nociceptive fibers of the remaining colon (and of pelvic viscera) travel in part through the superior hypogastric plexus and lumbar splanchnic nerves to reach the spinal cord. The superior hypogastric plexus is a flattened band of intercommunicating fibers continuous with the intermesenteric plexus. It is found retroperitoneal and caudad to the inferior mesenteric artery near the abdominal aortic bifurcation, at the level of the L5/S1 vertebral junction. Since it carries not only sympathetic efferent fibers but also visceral afferent fibers from these abdominopelvic structures, the superior hypogastric plexus serves as a target in interventional pain medicine for visceral analgesia of the distal colon and pelvic viscera.

The pelvic splanchnic nerves (nervi erigentes) arise from S2 to S4 ventral rami and contribute parasympathetic fibers to the inferior hypogastric plexus (also called the pelvic plexus), where they continue through to ganglia in close proximity to

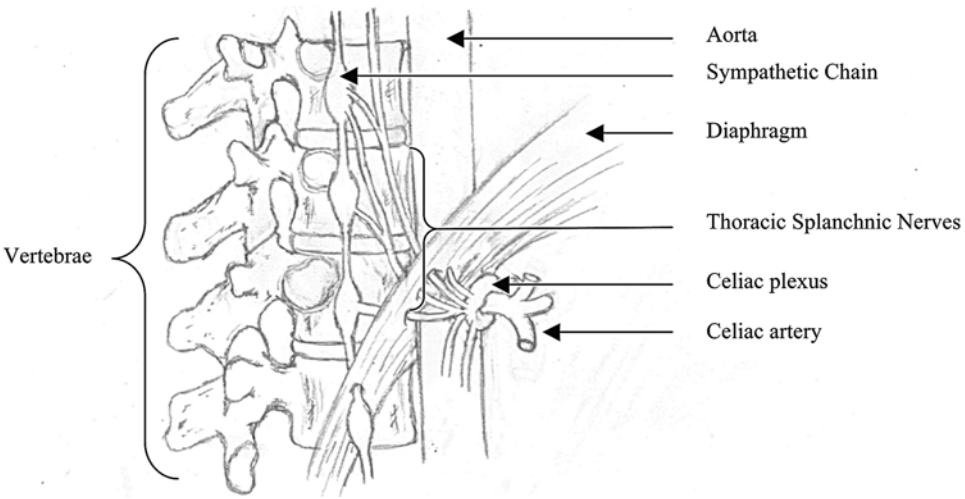

Fig. 13.1 Celiac plexus parasagittal anatomy

the target pelvic viscera. This parasympathetic autonomic route also serves as another afferent visceral pathway.

The vagus nerve also carries visceral afferent information to the central nervous system (with associated cell bodies residing in the nodose ganglia); however, this information is thought to be for autonomic (parasympathetic) regulation, primarily. It is unclear at this time the degree to which, if any, the vagus afferent pathway is related to visceral nociception. There is evidence to suggest that vagal nerve stimulation may attenuate both somatic and visceral pain, possibly through descending inhibitory influences on the spinal dorsal horn neuron responses [11, 12].

The reader should also be aware of the existence of the enteric nervous system, which is the intrinsic nervous system of the gastrointestinal tract that functions autonomously to regulate autonomic gut function.

Sensitization of Visceral Afferents

Visceral afferent nociceptive pathways, as is the case with somatic afferents, may undergo sensitization after disease or inflammation. A general state of neuronal hyperexcitability results in decreased thresholds for firing, increased number of suprathreshold responses, and an increase in spontaneous electrical activity [13].

Visceral Pain Due to Abdominal Malignancy

Tumor burden from primary or metastatic disease may result in visceral pain through a number of mechanisms. For instance, visceral nociceptors respond to noxious mechanical stretch. This can occur in the setting of tumor growth in solid organ parenchymata, causing capsular distention, or in hollow organs, causing narrowing or obstruction with proximal tissue stretch. Ischemia from tumor invasion or compression of blood supply leads to an inflammatory response, characterized by the release of inflammatory mediators such as prostaglandins, bradykinin, and cytokines. This can in turn sensitize the visceral afferent system, amplifying nociception both peripherally and centrally. Neuropathic-type pain is due to compression or dysfunction of neural structures from direct or indirect tumor involvement. Visceral pain can be sequelae of cancer treatment as well, since there is often significant alteration in both structure and function of involved treatment areas. The following sections describe select cancer-related abdominal pain states both from tumor and in survivorship.

Select Abdominal Cancer Pain States

Gastric Pain

For the year 2013, the estimated new cases of stomach cancer in the USA is over 21,000, per SEER [2]. The majority (90 %) of gastric cancer type is adenocarcinoma. Risk factors for stomach cancer include the presence of *Helicobacter pylori* infection, chronic gastritis, and lifestyle factors (such as smoking or consuming smoked and pickled foods) [14].

Gastric cancer patients complain of burning and dull pain along the epigastrium or left upper abdomen. Tumor burden produces pain from distention, ischemia, compression, erosion, inflammation, and obstruction of the stomach and surrounding structures. Gastric and gastroesophageal (GE) junction cancer pain is managed primarily with a combination of nonopioid analgesics, opioid analgesics, and adjuvants, per World Health Organization (WHO) Analgesic Ladder guidelines [15]. Abdominal pain from gastric and GE junction cancer can also be managed by interventional pain techniques [3, 16, 17] such as thoracic splanchnic neurolysis or celiac plexus neurolysis, with absolute alcohol or 10 % phenol (in 20 % glycerin) as the neurolytic agent.

Treatment for primary gastric cancer depends on the TNM (Tumor, Node, and Metastasis) staging [18]. Radical surgery (subtotal or total gastrectomy with omentobursectomy and lymph node dissection) is the standard therapy for local disease, although neoadjuvant or adjuvant chemotherapy and/or radiation therapy may also be part of the treatment plan.

Hepatobiliary Pain

The estimated year 2013 incidence for hepatobiliary cancer in the USA is over 30,000 [2]. Hepatocellular carcinoma accounts for 90 % of all cases of primary liver cancer. Hepatitis viral infection (both hepatitis B and C) as well as hepatic cirrhosis from heavy alcohol consumption often precedes the diagnosis of liver cancer. Other associated risk factors include tobacco use and consumption of food contaminated with aflatoxins (metabolites produced from *Aspergillus* fungal strains) [1].

Gallbladder (and biliary tree) cancer, on the other hand, is less common, with year 2013 estimates for US incidence at approximately 10,000, nearly all adenocarcinomas [2]. Specific risk factors for both gallbladder and bile duct cancer have been identified as increased body mass index and cholelithiasis.

Visceral nociceptors found along the liver capsule, vasculature, and biliary system are activated by tumor growth through hepatic capsular distention, hepatobiliary duct obstruction, and vascular (portal vein or hepatic vein) obstruction. Patients describe the pain as located about the right side of the abdomen. It may be continuous or colicky. Pain may refer to the back or to the right shoulder, when diaphragmatic irritation occurs (this is referred pain via convergence of visceral and somatic afferents in the spinal cord dorsal horn).

Hepatobiliary cancer pain is managed primarily with a combination of nonopioid analgesics, opioid analgesics, and adjuvants, per WHO Analgesic Ladder guidelines. Patients with abdominal pain from hepatobiliary cancers may be candidates for thoracic splanchnic neurolysis or celiac plexus neurolysis with absolute alcohol or 10 % phenol (in 20 % glycerin) [19].

In patients with localized liver cancer, surgical resection is the recommended treatment. Depending on TNM staging, radiotherapy and/or chemotherapy systemically or via hepatic arterial infusion (HAI) may also be offered. Chemoembolization employs both HAI and distal hepatic arterial vessel occlusion (to increase regional drug distribution and dwell time in the tumor) by a number of materials, such as gelatin sponge, collagen, polyvinyl alcohol, starch microspheres, etc. and can be associated with abdominal pain during infusion. Local gallbladder cancer and bile duct cancer (cholangiocarcinoma) may be amenable to surgical resection; otherwise, unresectable disease may be treated with adjuvant chemotherapy and radiotherapy.

Pancreatic Pain

In 2013, over 45,000 people in the USA are diagnosed with pancreatic cancer. It is the fifth most common cause of cancer-related deaths in the USA [2]. Over 90 % of pancreatic cancers are ductal adenocarcinomas. Pancreatic cancer is associated with chronic pancreatitis, diabetes, smoking, obesity, and heavy alcohol use.

Patients with pancreatic cancer often complain of a dull epigastric pain radiating to the back. Visceral structures coaffected include the deep posterior abdominal wall, connective tissue, ducts, and vasculature. Pain is also attributed to associated bulky lymphadenopathy about the celiac axis.

Pancreatic cancer pain is managed primarily with a combination of nonopioid analgesics, opioids, and adjuvants, according to WHO Analgesic Ladder recommendations. Patients with abdominal pain from pancreatic cancer or pancreatitis often are good candidates for thoracic splanchnic neurolysis or celiac plexus neurolysis with absolute alcohol or 10 % phenol (in 20 % glycerin) [20, 21].

Surgical resection for pancreatic tumors is recommended for localized disease, although this accounts for less than one-fifth of patients at presentation [18]. Pancreatic cancer is generally considered resistant to standard chemotherapy and radiation therapy. Patients may be enrolled, however, in clinical trials.

Intestinal Pain

Cancer of the small intestines is relatively uncommon and accounts for less than 5 % of gastrointestinal malignancies. Colorectal cancer, however, is one of the *most* common cancers—in the year 2013 the number of those newly diagnosed in the USA with colon cancer is approximately 140,000, whereas the number for newly diagnosed rectal cancer is over 40,000 [2, 14]. Risk factors for colorectal cancer have been identified as follows: genetic predisposition, physical inactivity, high body mass index, high intake of alcohol and red meat, and low consumption of fruits and vegetables [1].

Patients with colorectal cancers present with pain from abdominal cramping and distention, and other symptoms such as bleeding. Treatment for abdominal pain from colorectal carcinoma includes standard therapy through WHO Analgesic Ladder guidelines. In addition, specific interventional pain techniques for the management of colorectal pain consist of the following: celiac plexus neurolysis for pain arising from small bowel cancer or large bowel cancer proximal to the colonic splenic flexure; superior hypogastric neurolysis for pain arising from colon cancer distal to the splenic flexure; and ganglion impar block for distal rectal pain [3, 22–24].

Surgical resection of primary tumor and adjuvant chemotherapy is the general treatment plan for local colorectal carcinoma [18]. For advanced disease treatment, algorithms become more complex in order to address widespread metastatic disease.

Peritoneal-Related Pain

Peritoneal carcinomatosis occurs when abdominal cancer spreads to the peritoneum. Peritoneal carcinomatosis can therefore cause diffuse abdominal pain through inflammation, adhesions between tumor and surrounding tissue with resultant stretching and stricture, and ascites with abdominal distention. Intraperitoneal chemotherapy as treatment for abdominopelvic malignancy produces a painful chemical serositis experienced by up to half of those treated [3].

Select Abdominal Pain States in Cancer Survivorship

Cancer survivors may continue to experience persistent pain beyond the course of the disease and its related treatment. Up to one-half of cancer survivors experience ongoing pain after

cancer treatment [4, 17]. Iatrogenic visceral pain from mechanical, ischemic, inflammatory, and neuropathic insult to tissue and nerves in the treatment field is seen after surgery, chemotherapy, radiation therapy, and other modalities. This damage may lead to chronic somatic-nociceptive, visceral-nociceptive, and neuropathic pain, as well as sympathetically maintained pain.

There exist a number of chronic abdominal pain conditions experienced by cancer survivors who have undergone treatment for malignant disease, examples of which are described in the following text.

Gastrointestinal Graft-Versus-Host Disease

Hematopoietic stem cell transplantation (HSCT) is a procedure used to treat certain blood cancers. The procedure involves depleting or eradicating the recipient bone marrow with chemotherapy and/or radiation therapy and then repopulating the bone marrow by transplanting autologous or allogeneic hematopoietic stem cells. HSCT is associated with significant morbidity to include infection, mucositis, and graft-versus-host disease (GVHD), to name a few. GVHD is explained in basic terms as the donor bone marrow immune cells identifying the host tissue as foreign and subsequently mounting an immune attack against the host tissue. This condition or one indistinguishable to it may actually be seen in both autologous and allogeneic transplantation [25]. GVHD may become a chronic (defined as 100 days posttransplant) inflammatory condition, commonly affecting skin, liver, and the gastrointestinal tract [26]. GVHD has been known to cause chronic abdominal pain states in cancer survivors due to frequent, recurrent loose stools, nausea/vomiting, and abdominal cramping with distention. Both acute and chronic GVHD are generally managed with steroids and other immunosuppressive agents [27, 28].

Radiation Enteritis

The intent of radiation therapy for malignancy is either to cure primary or metastatic disease or to palliate symptoms associated with disease. This treatment modality employs high-energy radiation, which can be applied through external sources (external beam radiation therapy) or through radioactive material placed in the body (brachytherapy) or bloodstream (systemic). Radiation targets the cellular DNA of rapidly dividing malignant cells, leading to impairment in cell division and cell death.

Intestinal mucosal cells also undergo rapid turnover and therefore are at risk for damage by radiation. Radiation therapy side effects can occur during the treatment course (early) or months to years after treatment (late) [29–32]. Examples of radiotherapy side effects involving the abdomen include radiation dermatitis, gastroenteritis, bacterial overgrowth with resultant malabsorption, ulceration, perforation, fibrosis and stricture leading possibly to obstruction, and fistula formation. Patients may experience abdominal complaints, such as painful cramping, loose stools, nausea/vomiting, and anorexia, both during and after radiation therapy. These symptoms are managed conservatively through proper skin care, dietary modifications, antimotility and antiemetic agents, and analgesics. In some cases, surgical intervention for the affected bowel is indicated.

Chronic Abdominal Pain After Cancer Surgery

Iatrogenic tissue and nerve injury and other complications arise at times from surgical tumor resection. Abdominal surgery for malignancy may entail tumor resection or debulking, often sacrificing or altering adjacent healthy tissue and nerves. Acute postoperative pain usually resolves over days to weeks; however, painful neuroma formation, scarring, fibrosis, and stricture formation along the involved abdomen/abdominal wall may ensue. Development of postsurgical intra-abdominal adhesions could contribute to chronic abdominal pain from mesenteric stretching, gut narrowing or obstruction.

Conclusion

Cancer-related abdominal pain is sequelae of both the underlying malignant process and the cancer treatment modality. Abdominal somatic, visceral, and nerve structures affected can produce a nociceptive, neuropathic, or mixed pain state.

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