Current management of pancreatic cancer

Introduction

Pancreatic cancer is increasing in India. 15000 to 17000 new cases are seen every year. Prognosis of pancreatic cancer is dismal. 80% patients are diagnosed at an advanced stage. Average 1year survival across all stages is only 20%. Median survival for locally advanced disease is just 6-10 months and in patients with metastatic disease this falls to 3-6 mo. Overall 5 year survival is less than 4%.

Early stage patients can expect up to 40% 5-year survival after radical surgery. Hence early diagnosis & treatment is vital. Radical surgery is not advisable in advanced stage of disease. Aggressive chemo radiotherapy is offered in advanced stage. Newer modalities are under trial for treatment of locally advanced and metastatic disease.

I am presenting here an interesting case for readers and will then discuss current treatment for pancreatic cancer.

Case report:

A 74-year-old patient with obstructive jaundice was diagnosed to have tumor in the head & neck of pancreas on CT scan of abdomen. Tumor was abutting Portal Vein (PV). (PIC 1) A EUS guided biopsy was done. It showed a poorly differentiated pancreatic ductal adenocarcinoma (PDAC). In view of the suspicious vascular involvement & poor differentiation, systemic chemotherapy was planned as initial treatment. Since patient was deeply jaundiced, she underwent an ERCP and a 10 F plastic stent was inserted in the bile duct. When bilirubin came to normal, chemotherapy was started using gemcitabine as the main drug. Repeat imaging after 3 cycles showed good response and patient underwent surgery. Whiple’s pancreatoduodenectomy (PD) was done. (Pic 2) Postoperatively patient received chemotherapy again. Patient did well and lived for 2 & 1/2 years.

Discussion

Pancreatic cancer is a leading cause of cancer death worldwide and is on the rise in India too. The incidence is approximately 2 per 100,000 in India. Advanced age, male sex, smoking, alcoholism, chronic pancreatitis, diabetes, obesity, fatty diet, exposure to toxic chemicals (occupational hazard), genetic mutations, family history of pancreatic cancer are major risk factors for pancreatic cancer.

Pathology

Important pathological subtypes of pancreatic cancer are given in table 1. Almost 90 % of pancreatic cancers are pancreatic ductal adenocarcinoma (PDAC) and further discussion is focused on PDAC. Cystic tumors and NET are separate topics of discussion.

Table1

<table>
<thead>
<tr>
<th>Adenocarcinoma (PDAC),</th>
<th>Neuroendocrine Tumor (NET),</th>
<th>Cystic Tumor</th>
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<tr>
<td></td>
<td></td>
<td>Lymphoma</td>
</tr>
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<td></td>
<td></td>
<td>Metastasis</td>
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PDAC can occur in any part of pancreas. However it is more frequent in the head, uncinate process & neck (right side) of pancreas than body & tail (left side) of pancreas. The clinical presentation varies depending on the part involved. Table 2 gives a list of presentations. PDAC located in body and tail usually presents late.
Table 2

<table>
<thead>
<tr>
<th>Clinical presentation</th>
<th>Right</th>
<th>Left</th>
<th>Uncommon</th>
<th>Right</th>
<th>Left</th>
<th>Uncommon</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jaundice, Dark urine</td>
<td>Acute pancreatitis</td>
<td>Back pain</td>
<td>Jaundice (late)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pale white stools</td>
<td>Acute cholangitis</td>
<td>Mild pancreatitis</td>
<td>Incidental pick up</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal &amp; back pain</td>
<td>(Fever, jaundice, abdominal pain)</td>
<td>Unexplained Weight loss, anorexia, nausea, vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea, vomiting, weight loss, anorexia</td>
<td>Sudden onset / worsening diabetes</td>
<td>Sudden onset / worsening diabetes</td>
<td></td>
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<td></td>
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<tr>
<td>Palpable GB</td>
<td>Incidental pick up</td>
<td>Metastasis (ascites, liver)</td>
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<tr>
<td>Metastasis (ascites, liver)</td>
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</table>

Screening of asymptomatic individuals for pancreatic cancer is not recommended. Screening modalities (USG, MRCP, CT, EUS, serum CA19-9 levels) have limitations and are expensive. However high risk individuals (multiple risk factors present) should be kept under surveillance using some of these modalities. Researchers are working on detection of cancer biomarkers (DNA, mRNA, HIP/PAP) in the pancreatic juice, however none is recommended yet for use in clinical practice.

Work-up of a patient with suspected pancreatic tumor is shown in table 3. Patients may have raised direct bilirubin & alkaline phosphatase (s/o biliary obstruction); raised WBC counts & transaminases (s/o cholangitis). Amylase and lipase also may be elevated. CA19-9 levels may or may not be elevated and serial estimation may be required. Triple phase contrast enhanced CT scan or MRI of abdomen forms the backbone of diagnosis and staging of pancreatic cancer. A EUS is useful for diagnosis, staging and biopsy. An ERCP and bile duct stenting is needed only when patient is deeply jaundiced or has acute cholangitis. ERCP does not have a diagnostic role. Occasionally a PET-CT is required. A biopsy and PET-CT is important to differentiate cancer from benign lesions like focal pancreatitis & autoimmune pancreatitis (AIP). A rise in serum levels of IgG 4 indicates AIP.

Table 3

<table>
<thead>
<tr>
<th>Blood tests</th>
<th>Abdominal Imaging</th>
<th>Endoscopy</th>
</tr>
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<tbody>
<tr>
<td>CBC, BUN, creatinin, BS, HbA1C, LFT, CA19-9, amylase, lipase</td>
<td>USG Triple phase CT MRCP &amp; Triple phase MRI PET / PET-CT</td>
<td>Endoscopic Ultrasound (EUS) + biopsy Endoscopic Retrograde Cholangio-Pancreatography (ERCP)</td>
</tr>
</tbody>
</table>

A percutaneous biopsy should be avoided in potentially resectable patients and should be done only in cases of metastasis. A histopathological/biopsy confirmation is desirable but not mandatory in all cases. Staging laparoscopy has limited role in PDAC of head /neck and is recommended in selective cases with borderline resectable & locally advanced tumor (see below). However it is a routine procedure prior to surgery for left sided PDAC as they are diagnosed at a later/advanced stage and a laparoscopy can prevent an unnecessary laparotomy.

A simplified staging and treatment of PDAC is given in Table 4. It is based on tumor extent.

Surgery, chemotherapy, radiotherapy & palliative measures are used in combination depending on stage of disease. Chemotherapy and radiotherapy can be used in both pre-op and post-operative period.

A resectable PDAC in an otherwise fit patient is treated by a curative surgery. A variable portion of pancreas is removed depending on tumor location. For a right-sided tumor pancreateoduodenectomy or Whipple’s operation is performed. It involves radical resection of tumor bearing head of pancreas with attached duodenum with or without part of stomach (classical vs. pylorus preserving—PPPD respectively), a length of common bile duct, gall bladder and draining lymph nodes. This is followed by an equally demanding reconstruction by anastomosing a Roux loop of jejunum to pancreas, bile duct and stomach in the same sequence. In some patients reconstruction technique is modified and pancreas is joined to stomach. Rate of postoperative complications, length of hospital stay and survival after the original and modified procedures are similar. Reconstruction technique is at the surgeon’s discretion. Postoperative bleeding, pancreatic anastomotic leak, pancreatic fistula, biliary anastomotic leak and a delayed gastric emptying are common complications after a pancreateoduodenectomy. Leaked pancreatic juice is responsible for other complications in most situations.
Surgery alone has not improved 5-year survival and therefore adjuvant (postoperative) and sometimes neoadjuvant (preoperative) therapy in the form of chemo +/- radiation therapy, is proposed. This has shown to improve survival. Though neoadjuvant therapy is not a routine in for left sided tumor a distal (neck to tail) pancreatectomy is done. It is accompanied by local nodal clearance with or without surrounding organs like spleen, stomach, colon, adrenal & kidney. Involvement of celiac & superior mesenteric artery and Para-aortic LN are contraindications to any curative surgery. Sometimes a total or subtotal pancreatectomy is done for extensive or multifocal tumor or when intraoperative frozen section shows a positive margin.

Surgery alone has not improved 5-year survival and therefore adjuvant (postoperative) and sometimes neoadjuvant (preoperative) therapy in the form of chemo +/- radiation therapy, is proposed. This has shown to improve survival. Though neoadjuvant therapy is not a routine in PDAC prior to a curative surgery, adjuvant therapy is a rule. Adjuvant therapy is also given when margins are positive for cancer on histopathological examination. Gemcitabine is the drug of choice for neoadjuvant & adjuvant chemotherapy. Adjuvant External beam radiotherapy (EBRT) is given in a dose of 1.8-2Gy per day, 5 times a week for a total of 50Gy. During surgery tumor bed is marked with clips to minimize radiation damage to surrounding organs later. Select units even give high dose intraoperative radiation (IORT) to the tumor bed. Monoclonal antibodies and anti-angiogenic factors are being tried along with other agents. Similarly newer radiotherapy options like 3-D conformal, image guided (IGRT) and intensity modulated (IMRT) are available. These give higher dose to tumor bearing area & lesser dose to surrounding organs like liver, spinal cord, and duodenum etcetera. This improves results but reduce side effects. Pre, intra & post-operative chemotherapy, symptom palliation and Local ablation are initiated simultaneously. If chemo radiotherapy lowers the tumor stage (down staging), a curative surgery is sometimes attempted. A search is on for ideal and optimum adjuvant and neoadjuvant chemo & radiotherapy regimens, drugs & delivery systems. Newer drugs like monoclonal antibodies and anti-angiogenic factors are being tried along with other agents. Similarly newer radiotherapy options like 3-D conformal, image guided (IGRT) and intensity modulated (IMRT) are available. These give higher dose to tumor bearing area & lesser dose to surrounding organs like liver, spinal cord, and duodenum etcetera. This improves results but reduce side effects. Pre, intra & post-operative radiation help in reducing loco regional tumor recurrence and improve survival. All neoadjuvant therapies increase risk of postoperative complications especially pancreatic anastomotic leak and bleeding.

Borderline resectable tumors may require an additional resection of part of hepatic artery, portal vein or superior mesenteric vein and reconstruction. Portal or superior mesenteric vein & Hepatic artery may get involved in the tumor because of their close proximity to a tumor located in head, neck or proximal body. In that case a portion of the vessel is resected and reconstructed. Involvement of these vessels has not shown to reduce survival if a successful resection is achieved. However when superior mesenteric artery (SMA) or celiac artery (CA) is involved, its resection and reconstruction does not show survival advantage, hence is not recommended.

Maximum research currently is focused on LAPC as this group comprises of a large section of PDAC and improving their survival could be a game changer. These are usually stage III tumors in formal staging and are not resectable. Treatment is aimed at palliation of complaints like obstructive jaundice, abdominal pain or gastro duodenal obstruction. Specific tumor directed therapies like chemotherapy, radiotherapy & tumor ablation are initiated simultaneously. If chemo radiotherapy lowers the tumor stage (down staging), a curative surgery is sometimes attempted.

Jaundice and gastro duodenal obstruction needs to be relieved prior to any down staging attempts. Jaundice is relieved by endoscopic or percutaneous trans hepatic biliary stenting. Endoscopic route is the preferred option. A 10F plastic stent or a self-expandable metal stent (SEMS) is inserted. It establishes natural internal biliary drainage. Plastic stent has higher chance of blockade. When endoscopy is not feasible or fails, a percutaneous route is used for internal drainage. Gastro duodenal obstruction can be relieved by an endoscopic pyloroduodenal stenting. When non-operative palliation of bile duct or bowel obstruction is not possible or a locally advanced tumor is detected during operation for presumed resectable tumor, a surgical palliation is done in the form of a biliary enteric bypass (hepaticojejunostomy) and gastro duodenal bypass (gastrojejunostomy).
Abdominal and back pain, which is due to pancreatic ductal obstruction and infiltration of peripancreatic nerves is relieved using paracetamol & opioid analgesic (tramadol, pentazocine) tablets, transdermal drug delivery patches (diclofenac, fentanyl or buprenorphine) and celiac ganglion blockade (CT guided / EUS guided / during open surgery / thoracoscopy). Sometimes EBRT is used for pain relief.

When above measures are completed or are not needed, tumor directed therapy is initiated in the form of chemotherapy or chemo radiation. Again Gemcitabine is the most commonly used chemotherapy agent, however a combination with other chemotherapy agents (e.g. FOLFIROXIN, nab-paclitaxel) can further improve overall survival than gemcitabine monotherapy. Chemotherapy agents and dosage, radiotherapy dosage, modes of radiotherapy are undergoing continuous evolution. Induction chemotherapy followed by Chemo radiation is preferred over chemotherapy alone or concurrent chemo radiation. The response to therapy is assessed using CT scan, PET-CT scan & tumor marker like CA 19-9. If desired response is seen on CT / PET-CT scan (RECIST criteria) and there is reduction in CA19-9 levels then a surgical resection may be considered. The response to preoperative therapy is confirmed on histopathological examination by checking tumor regression grade if patient gets operated later. Because of inconsistent response, there is not a single strongly recommended regime and patients are best treated in a trial setting.

Given that very few patients with PDAC become suitable for curative surgery and most have only a limited response to chemotherapy; tumor debulking or interstitial ablation has been investigated as a potential additional therapy. Tumor debulking (R2 resection) has hardly shown statistically significant survival advantage (additional 1-3 mo.). But it has significant complications, longer hospital stay and higher mortality rate. Hence R2 resections are not recommended as part of the standard management of PDAC. It is usually an unfortunate accidental fall-out of a curative surgical attempt.

Primary tumor ablative therapies are delivered intraoperatively, percutaneously or endoscopically. They have become part of standard therapy in many other solid organ tumors. Early studies of local ablation in the pancreas were associated with high morbidity and mortality. However many of the early concerns that surrounded safety have been addressed with device development, modification of technique and combining the technology with high quality real-time imaging. This has reduced associated complications.

Various ablative modalities include radiofrequency ablation (RFA), photodynamic therapy (PDT), cryoablation, laser, high intensity focused ultrasound (HIFU), microwave, Ir-reversible electroproporation (IRE), Stereotactic Body Radiation Therapy (SBRT) & Iodine-125. Limitation is an unpredictable zone of ablation & complications like acute pancreatitis, surrounding organ injury, gastrointestinal hemorrhage, skin burns (HIFU) noticed with them. However with technical advances complications are few & zones are predictable. All strategies appear to be, useful, feasible and safe. However their use outside clinical studies is not recommended at this juncture. An attempt is made to combine these with chemotherapy.

RFA causes tissue destruction through the application of a high frequency alternating current that generates high local temperatures and a coagulative necrosis. The technique is widely used in hepatocellular carcinoma. For LAPC it is delivered intraoperatively or via percutaneous route or under EUS guidance. All studies have demonstrated that RFA leads to tumor necrosis and a decrease of tumor volume. Some studies have observed an improvement in tumor related symptoms like back pain, CA19-9 levels and overall survival in LAPC.

Cryoablation destroys a tumor through multiple freeze-thaw cycles. It is commonly performed intra-operatively under ultrasound guidance. It is combined with a palliative bypass surgery or endoscopic biliary and duodenal stenting. Effective control of pain, normalization of CA 19-9, improvement in performance status and prolongation of survival have all been reported following cryoablation. Rates of significant complications appear to be lower than in other methods of ablation.

Laser based ablative therapy or Photodynamic therapy (PDT) results in tumor ablation by exposure to light following an intravenous injection of a photosensitizer chemical, which is taken up by cells. Light is delivered via small optic fibers, which are positioned percutaneously under CT guidance or under EUS guidance.

Non-thermal, non-laser methods of ablation like High intensity focused ultrasound (HIFU) therapy, is a non-invasive method of ablation. Ultrasound energy from an extracorporeal source is focused on the pancreatic tumor to induce thermal destruction of tissue without affecting surrounding organs.

Irreversible electroproporation IRE or NanoKnife® (Angiodynamics, Inc., NY, United States) is an emerging non-thermal ablative technique which uses electrodes, placed in the tumor, to deliver direct current. This causes damage to cell membrane of the targeted tissue, which irreversibly damages the cell’s homeostatic mechanism, causing apoptosis. One of the major advantages of this technique is that it can be used in tumors that are in close proximity to peri-pancreatic vessels without risk of vascular trauma.

Systemic chemotherapy agents are associated with significant side effects, which can result in patients having to stop therapy or undergo dose reduction. Several groups have therefore explored using local anti-tumor agents in PDAC. They are instilled in the tumor tissue under EUS guidance.

In short, ablative therapies for unresectable pancreatic cancer are an attractive emerging therapy. Long-term survival data for many of the techniques is absent currently. Large prospective randomized studies will be required to assess the efficacy of these techniques and define their position in future treatment algorithms for the management of LAPC.

Patients having distant metastasis may have tumor deposits in liver, lung, bones, and peritoneum etcetera. They are not candidates for any curative surgery. Treatment is aimed at prolonging survival and improving quality of life. Hence chemotherapy, radiotherapy and nonoperative
Palliative measures form the backbone of treatment. These patients are weak, malnourished, have lost weight, are usually jaundiced and often not in a condition to tolerate strong treatments. Hence patients are carefully selected for treatment. Drugs like gemcitabine, capecitabine, 5-FU; cisplatin, oxaliplatin, irinotecan, erlotinib, paclitaxel & docetaxel are used in various combinations and dose adjustments. However treatment response is often poor and treatment toxicity high, forcing the treating team to abandon the treatment midway. Radiation Therapy is restricted to bone metastasis to relieve pain. Primary tumor targeted radiation is not useful at this stage.

A lot of research is going on in the role of targeted agents like human epidermal growth factor receptor (EGFR) inhibitor, angiogenesis inhibitors, signal transduction inhibitors, apoptotic activity modulators and eicosinoid pathway inhibitors. These attack selectively the tumor cells, thus reducing the side effects but increase clinical response compared to standard chemotherapy. Targeted agents may be used even in patients who would be otherwise unfit (poor performance status) for standard cytotoxic chemotherapy. Erlotinib, a tyrosine kinase inhibitor is one such agent. It has shown benefit in clinical trials when used alone or in combination with standard chemotherapy. They are also useful for tumors resistant to standard chemotherapy providing a second or 3rd line of defense. Very rarely surgery may be used for palliation in advanced stage.

Ablative therapies are being tested for metastatic tumors. In contrast to LAPC, no difference in overall survival was shown in patients with metastatic PDAC, following RFA treatment. Larger studies, in combination with systemic chemotherapy, are needed to evaluate potential role of RFA in patients with metastatic disease.

Currently the prognosis of PDAC is poor as shown in Table 5. Efforts are on to improve the prognosis and also bring a change in the nihilistic attitude towards pancreatic cancer.

### Table 5

<table>
<thead>
<tr>
<th>Simplified stage</th>
<th>distribution</th>
<th>Median survival (months)</th>
<th>5-year survival (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resectable &amp; BR</td>
<td>15-20%</td>
<td>15-20</td>
<td>15</td>
</tr>
<tr>
<td>LA</td>
<td>40%</td>
<td>-12</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Advanced</td>
<td>45%</td>
<td>3-6</td>
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</table>

In conclusion, pancreatic cancer is a bad disease to have. It has a poor prognosis especially in advanced stage. Early diagnosis is the key to longer survival. Radical surgery is the only curative treatment option. However surgery has reached its limits. Pre and postoperative chemoradiotherapy combination may prolong the disease free and overall survival. Local ablative therapy, though promising has yet to establish their place. Further research will bring more hope. Pancreatic cancer treatment is a multidisciplinary treatment involving HPB surgeon, GI endoscopist, interventional radiologist, medical oncologist, radiation oncologist and pain specialist. It is best to manage these patients at specialized centers.

**PEARLS & PITFALLS**

Pancreatic cancer is increasing in India

Most patients are diagnosed at a late stage and 1-year overall survival is only 20%.

Early diagnosis followed by surgery and a combination of chemo radiotherapy can increase the disease free and overall survival.

Male sex, smoking, diabetes, chronic pancreatitis, obesity & genetic mutations are important risk factors for pancreatic cancer.

90% pancreatic cancers are ductal adenocarcinomas.

Obstructive jaundice is the commonest presentation of cancer in the head of pancreas. However jaundice is a late occurrence if cancer is in the body-tail of pancreas.

Screening for pancreatic cancer is recommended only in individuals with multiple high risk factors.

USG abdomen & serum CA19-9 levels are not very sensitive screening tools. New methods like detection of biomarkers (DNA/mRNA/HIP/PAP) in pancreatic juice are promising.

Triple phase IV contrast CT scan or MRI of abdomen, Endoscopic Ultrasound (EUS) and PET-CT study are used for staging of a pancreatic cancer.

EUS guided biopsy is obtained whenever possible prior to surgery in resectable tumors. A percutaneous biopsy should be avoided in resectable tumors.

Chronic pancreatitis with inflammatory head mass formation, groove pancreatitis, focal acute pancreatitis of head with necrosis and focal autoimmune pancreatitis can masquerade as a pancreatic cancer.
A negative biopsy does not preclude a curative surgery when in doubt. In 5% of patients final histopathology may show a benign etiology.

ERCP (pancreatobiliary endoscopy) and biliary stenting (plastic / metal) is not necessary before every curative surgery even if patient has jaundice.

Biliary drainage is done only if patient is deeply jaundiced or is having acute cholangitis and sepsis.

Diagnostic laparoscopy prior to a laparotomy for tumors in the body/tail of pancreas may avoid unnecessary laparotomy. However it is not recommended as a routine.

Resectable tumor in the head of pancreas is treated with a pancreatoduodenectomy. (Whipple's).

Resectable patient in the body/tail of pancreas is treated with distal pancreatectomy with or without splenectomy.

Local draining lymph nodes are cleared with every curative resection. Sometimes organs like colon, stomach & spleen are also removed to achieve negative margins.

Additional resection and reconstruction of portal vein is done in selected patients. Involvement of portal vein does not affect survival. However resection and reconstruction of superior mesenteric artery and celiac artery is usually not done. It does not improve survival.

Use of preoperative chemotherapy (neoadjuvant) and postoperative chemo radiotherapy (adjuvant) is recommended to improve disease free & overall survival.

Gemcitabine is the most common drug used in chemotherapy. New agents like monoclonal antibodies (anti EGFR & anti-angiogenic factor receptor) are still under trial. A search is on for ideal chemotherapy agent/s for pancreatic cancer.

External Beam Radiotherapy (EBRT) has revolutionized pancreatic RT with the technical advances like intensity modulation (IMRT) & image guidance (IGRT). This has reduced the toxicity and improved efficacy.

Locally advanced pancreatic cancer-LAPC- (involving nearby important arteries and lymph nodes) is treated with chemotherapy, radiotherapy, pain management & palliative endoscopic or surgical procedures.

Occasionally locally advanced tumors are shrunken (down staging) with CT+RT and later a curative surgery is attempted.

Radiofrequency Ablation (RFA), SBRT, HIFU and Irreversible Electroporation (IEP) are new modalities being tried in patients with LAPC.

Patients with distant metastasis are given only palliative treatment directed towards relief of jaundice, gastro duodenal obstruction & abdominal & back pain.

Obstructive jaundice & duodenal obstruction is relieved by endoscopic stent insertion or rarely surgery.

Analgesic medications, EUS guided celiac ganglion block & radiation are used to control pain.

Pancreatic cancer treatment is a multidisciplinary treatment involving HPB surgeon, GI endoscopist, interventional radiologist, medical oncologist, radiation oncologist and pain specialist. It is best to manage these patients at specialized centers.

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