Pancreatic Adenocarcinoma Decision Guide

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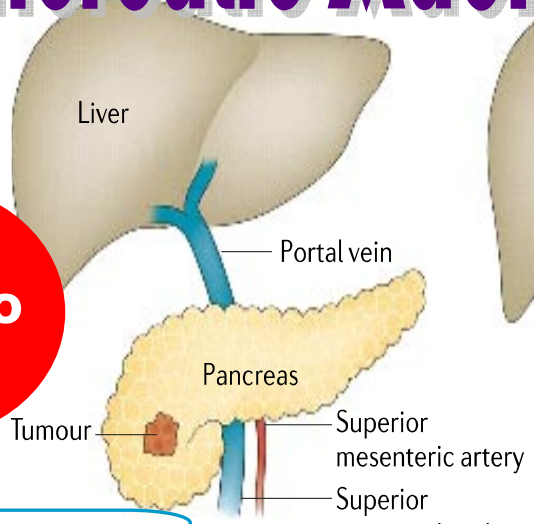


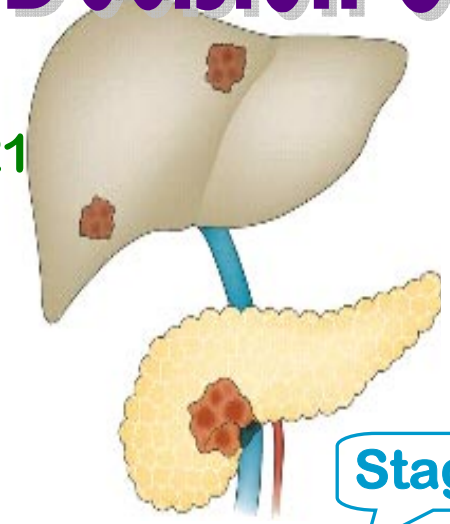


Figure 1

is a Fair Use reproduction of Figure 1 which appears in the June 2018 journal article *Therapeutic Developments in Pancreatic Cancer: Current and Future Perspectives*.

Stages 1 & 2A | **Stage 3** | **Stage 4**

Resectable | **Borderline resectable and/or locally advanced unresectable** | **Metastatic**

Row 1

ECOG 0/1 (2) | ECOG 0/1 (2) | ECOG 0/1 | ECOG 0/1 (2) | ECOG 2 | ECOG >2

Row 2

Resection + adjuvant chemotherapy (G–C)* | Neoadjuvant chemotherapy (e.g. FOLFIRINOX or radiochemotherapy) | 1st line FOLFIRINOX* | 1st line nab-paclitaxel + gemcitabine* | 1st line gemcitabine* | Best supportive care

Stable and/or response | Progress | 2nd line gemcitabine (+ nab-paclitaxel) | 2nd line nal-irinotecan + 5-FU* (or oxaliplatin + 5-FU)*

Row 3

Exploration | Continued chemotherapy

Median survival	26 months (5-year survival 30%)	~12–18 months	~6–11 months	~11 months	~9 months	~6–8 months	<6 months

Figure 1 | **Suggested treatment algorithm for patients with pancreatic cancer.** Patients are stratified according to tumour stage (resectable, borderline resectable and locally advanced unresectable, metastatic) and performance status (defined by the Eastern Cooperative Oncology Group (ECOG) score).

Median survival values are estimates from published data, mainly from small, single- arm or retrospective trials. In the metastatic setting, survival data are from trials of first-line therapy. This treatment algorithm represents the expert opinion of the authors [the authors of the article from which **Figure 1** was taken]. *Approaches are based on evidence from Randomized Controlled Trials. Other depicted treatment algorithms are current approaches, but they are not evidence-based and are not standard of care worldwide. Published in Springer *Nature Reviews Gastroenterology & Hepatology*, June 2018 and downloadable here.

Glossary			
ECOG	See **Table 1** to the right	**FFX**	FOLFIRINOX
NabP	Nab-Paclitaxel	**G+Cap**	Gemcitabine+Capecitabine
Neo-adjuvant	Therapy before surgery; **Adjuvant** is after surgery	**Backbone Therapy**	Best standard regimens, often FFX & NabP+Gem (NG)
1st Line Therapy	First regimen, followed by 2nd & 3rd Line regimens	**Phase, trial**	1 of 3 human research studies for evaluating therapies
Resection	Surgical removal of organs & allied structures, part or whole	**ASCO**	American Society of Clinical Oncology
Regimen	Also called a protocol, a combination of chemo agents & their dose schedules, eg. FFX.	**Stage, disease**	Degree of disease advancement. Each stage has substages. See the NCCN Guide

Table 1: ECOG Performance Status*

Grade	ECOG
0	Fully active, able to carry on all pre-disease performance without restriction
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
2	Ambulatory and capable of all selfcare but unable to carry out any work activities. Up and about more than 50% of waking hours
3	Capable of only limited selfcare, confined to bed or chair more than 50% of waking hours
4	Completely disabled. Cannot carry on any selfcare. Totally confined to bed or chair

* From *Toxicity And Response Criteria Of The Eastern Cooperative Oncology Group (ECOG), Am J Clin Oncol 5:649-655, 1982.*

Start Here – Introduction

The **Glossary** above defines some terms used in this **Guide**. For other terms and for many medical terms install free Wordweb. Once installed, place the cursor over an uncertain word, then Ctrl right-click to receive the definition. **Wordweb** works in any medium: Webpage, html, pdf, doc and most vector graphics.

There is hope. This **Decision Guide** will lead you to better care and decision-making. The **Guide**'s main features are the following:

- **Figure 1** on page-1 describes cautious treatment plans, which might be expected of many medical oncologists.
- Based upon disease Stage (1&2A, 3, 4) and patient Performance Status (**Row 1**: ECOG), **Figure 1** proposes reasonable treatment plans. But, those plans are limited to mainstay backbone chemotherapy regimens, which stop at Second Line Therapies (**Row 2**).
  - ► This **Decision Guide** remedies those defects by adding Third Line Therapies, **Table 2** below, a vital addition because many patients now reach that milestone due to better early therapies.
  - ► Further, **Table 2** offers wise Care Management strategies. And, each suggested option is supported by research, with the research documents made available to the reader by means of web links.
- **Figure 1**'s **Row 3** (Median Overall Survival) suggests the dire outcome, if the patient refuses to seize early control of his care and fails to utilize the opportunities and management strategies described in this **Decision Guide**.
- Like **Figure 1**, **ASCO** offers astute guides for Stage 1&2A cancer, Stage 3 and Stage 4, but they also fail to offer Third Line Therapies.

Footnotes: (1) In **Figure 1** the parenthetical (2) in ECOG 0/1 (**Row 1**) means *"for selected ECOG-2 patients."* And, the term "Progress" in the **Figure 1** flow path means disease progress, not patient progress.

(2) **Figure 1** is a summary of an excellent 2018 report, downloadable here, titled: *Therapeutic Developments in Pancreatic Cancer: Current and Future Perspectives*. It is authored by six specialists in surgical oncology, medical oncology and internal medicine at three European academic centers – two in Germany and one in the UK.

Comparing Figure 1 to Table 2

Carefully study the details of **Figure 1**. For each disease stage (Stages 1&2A, 3, 4) the figure offers a treatment plan (**Row 2**) based upon the patient's ECOG Performance Status (**Row 1**). ECOG classification details are given here.

Then, study **Table 2** below which expands the **Row 2** treatment plans (1) by adding **Care Management** strategies, (2) by proposing better-performing First Line and Second Line therapies, and (3) by suggesting Third Line Therapies.

Each column in **Table 2** (Stages 1&2A, 3, 4), corresponds to Stages 1&2A, 3, 4 in **Figure 1**.

Using the Guide, an Example

For example, if you expect a diagnosis of metastatic (Stage 4) pancreatic cancer, which is too likely, do the following:

1. In **Figure 1** review the Stage 4 column. There, the recommended therapy depends upon the patient's ECOG Performance Status (**Row 1**), that is, the recommended therapy depends on his ability to endure the given chemotherapy. Read about ECOG above.
2. According to **Figure 1**, if the patient is very strong (ECOG 0 or 1), he would begin with FOLFIRINOX, then when that fails he would switch to Nab-Paclitaxel + Gemcitabine (NG). But, there may be better approaches, based on recent research developments.
3. **Table 2** below offers improvements to the **Figure 1** and to **ASCO** recommendations (for Stage 1&2A cancer, Stage 3 and Stage 4):
   - 3.1. Promising therapy upgrades are offered to replace **Figure 1** and **ASCO** plans, and most upgrades don't require clinical trials.
   - 3.2. Third Line Therapies are proposed, something which **Figure 1** does not provide, nor do the **ASCO** and NCCN Guidelines.
   - 3.3. And **Table 2** offers a comprehensive management strategy for family caregivers, called Care Management.
4. The Bottom Line: **Figure 1**, **ASCO** plus **Table 2** COMBINED provide an in-depth **Decision Guide** with many potent options.

In the table IRE is Irreversible Electroporation. Its no-heat ablation process preserves blood vessels and ducts, an advantage over other ablation systems. IRE cannot treat lungs due to their gauzy structure. Nanoknife Surgery Warriors is an IRE support forum.

Updates

This **Decision Guide** is updated regularly and is available here. Submit proposed corrections or improvements to **EndPC**.

Table 2 is not the work of a medical institution. The author is a meticulous follower of pancreatic cancer developments, the chief care manager for several lethal cancer cases and a developer of care management strategies. He is the creator of the **EndPC** website.

Table 2
Hit Hard & Hit Early: The Following are Changes to Figure 1

	Stages 1&2A Resectable	Stage 3: Borderline & Locally Advanced	Stage 4 Metastatic
Care Mgt	● Maintain a sense of URGENCY. This is a swiftly moving parade. One misstep and you cannot go back and take a road previously forsaken. Your research and hard work are critical. No one will do it for you, no matter how celebrated your medical team. ● Financial Help: Travel & Support (Angel Flight, CancerNet), Charity (CancerCare), Drugs (ask manufacturer's assistance team).		
	● For Stages 1 & 2A employ only Note 1, Note 2 & Preface	● For Stage 3 employ only Note 1, Note 3 & Preface.	● For Stage 4, employ only Note 1, Note 4 & Preface, beginning on page 7.

1st Line Therapy

Substitute the following for **Figure 1** therapy and for **ASCO**'s Stages 1&2 guide.

- For resectable Asians an S-1 regimen might outperform surgery. See this report.
- Consider starting with the NabP+Gem (NG) Neoadjuvant regimen, but add Cisplatin, perhaps via the PAXG regimen. Gemcitabine+Cisplatin is better than FOLFIRINOX, if the BRCA mutation is present.
  - ▶ Cisplatin requires hydration, but saline IV can pose a danger. Avoid Wrong IV Bag.
- Induction NG will allow the use of mFFX after surgery, the preferred Adjuvant Therapy, followed by the best maintenance therapy: Gemcitabine + Capecitabine.
  - ▶ According to breakthrough research reported in 2018, mFFX increased Overall Survival from 34.0 to 54.5 months, compared to Gemcitabine monotherapy, the previous adjuvant AND maintenance standard. Therapy starts in week 3-12.
  - ▶ Progression Free Survival increased from 12.8 to 21.6 months. Details here.
- Post-surgery HAI + Gemcitabine might rival mFFX.
- Employ IRE as part of intra-operative surgery to manage tumor-encased blood vessels and surgical margins. Consider this fine USA IRE trial.

Substitute the following for **Figure 1** therapy and for **ASCO**'s Stage 3 guide.

- Initial (induction) therapy might be NabP+Gem (NG), plus Cisplatin, perhaps via the PAXG regimen. Gemcitabine+Cisplatin is better than FOLFIRINOX, if the BRCA mutation is present.
- Or to NG consider adding Cisplatin, Nivolumab, Anakinra & Paricalcitol (a synthetic Vitamin D) in ways described by Abstract 358 & Abstract 449 of the **2018 ASCO GI Symposium**, discussed here.
  - ▶ Anakinra curbs inflammation, a cancer driver, but Vitamin D's benefit is unsure.
  - ▶ Cisplatin requires hydration. Avoid Wrong IV Bag.
  - ▶ All components are available outside a Clinical Trial.
- Post-resection HAI + Gemcitabine might rival mFFX.
- Before employing radiation, use IRE to manage tumor-encased blood vessels and surgical margins. Consider this fine USA IRE trial.
- If radiation is wanted, consider Proton Therapy, which (unlike photon Xrays) causes negligible collateral damage. Xrays can cause pancreatitis, ulceration, enteritis, gut obstruction, ascites – risking fatal therapy delays. Florida & Massachusetts Proton centers have pancreatic programs.

In this section both 1st and 2nd Line Therapies are detailed, because it's not certain which chemo regimen will be employed first. The following strategy applies to both therapy lines. 3rd Line is later.

Generally, follow **Figure 1** and the **ASCO** Stage 4 guide, according to patient Performance Status (ECOG). But, as Note 4 urges:
(1) Immediately consider upgrades to two backbone therapies, NabP+Gem (NG) and FFX (as noted below), to increase impact.
(2) And give urgent priority to backbone-based Clinical Trials and to the Chemotherapy, Emerging Agents and Other Regimens lists.

This needs to be taken seriously. Hit Hard and Hit Early. There are no second chances with this disease. Choose the wrong path and time is lost; mutations proceed; micro-metastases propagate.

FFX is the preferred initial therapy. But, BRCA patients may do better on Gemcitabine+Cisplatin (G+C). Study all Emerging Therapies.

And, here are good ways to enhance standard therapy:

- Consider these variants, all available outside of a Clinical Trial:
  - ▶ Which sequence is better, NabP/Gem (NG) + NabP/Gem (NG) or NabP/Gem (NG) + FFX? Research suggests the answer here.
  - ▶ Is FOLFIRI better than FFX & FOLFOX? Review this research.
  - ▶ mFFX may be better than FFX. Research offers this evidence.
  - ▶ Added PEG-G-CSF may boost FFX performance. Details here.
- Consider NabP+Gem upgrades – No Clinical Trial is required.
  - ▶ Add Cisplatin, which performed well in small Clinical Trials.
  - ▶ Abstract 358 & Abstract 449 of the 2018 ASCO GI Symposium report good performance from regimens which add Cisplatin, Nivolumab, Anakinra and Paricalcitol (Vitamin D) to NabP+Gem.
  - ▶ Anakinra, an arthritis drug, curbs inflammation, a cancer driver. But, Vitamin D's benefit is uncertain.
  - ▶ And consider the new PAXG regimen; download report here.
  - ▶ Cisplatin requires hydration; so read about the Wrong IV Bag. Compared to saline "Balanced crystalloid fluids" save lives.
- BRCA patients: Consider Rucaparib or Olaparib after FFX or G+C.
- A new paradigm: Metastases removal is justified if few, yielding reduced tumor and chemotherapy burden and increased survival.
  - ▶ If there are ≤3 metastases in one organ (liver or lung) consider this approach, available for some patients. Lung-only patients often fare better. For liver-only see this emerging CAR-T therapy.
  - ▶ If Peritoneal metastases are present consider this therapy.
  - ▶ Lymph Node metastases are treatable, a method detailed here.
  - ▶ Spine metastases are treated at some Proton Therapy centers.
- Third Line therapy is addressed on Page 6, below.

2nd Line Therapy

Substitute the following for **Figure 1**'s 2nd Line Therapy and **ASCO**'s Stages 1 & 2 guide.

- For Adjuvant (post-resection) Chemotherapy use modified FFX (mFFX), which, according to recent research, produced an Overall Survival of 54.5 months, compared to 34.0 months for Gemcitabine, the previous adjuvant standard. More details here.
- For Maintenance Therapy (post-Adjuvant) use Gemcitabine+Capecitabine (G+Cap).
  - ▶ In 2015 the Adjuvant AND maintenance therapy was Gemcitabine alone (monotherapy). But, **Figure 1** is not aware of the new mFFX Adjuvant standard, instead advocating G+Cap.
- BRCA-defect patients might follow FFX (or Gemcitabine+Cisplatin) with single-agent Rucaparib for maintenance, although G+Cap is the current standard.

Substitute the following for **Figure 1**'s 2nd Line Therapy and **ASCO**'s Stage 3 guide.

- Radiation may NOT benefit metastatic patients, see Abstract e16257 here. And it does not benefit R1 resection patients. Study the report and the review: Radiation Fails.
- For Adjuvant Chemotherapy use Modified FFX (mFFX).
  - ▶ According to breakthrough research reported in 2018, mFFX increased Median Overall Survival by 61%, from 34.0 to 54.5 months over Gemcitabine alone, the previous adjuvant and maintenance standard.
  - ▶ Median Progression Free Survival increased 69%, from 12.8 to 21.6 months,
- For Maintenance Therapy use Gemcitabine + Capecitabine (G+Cap).
- BRCA-defect patients might follow FFX (or Gemcitabine+Cisplatin) with single-agent Rucaparib for maintenance, although G+Cap is the current standard.

Attention

In this **Decision Guide** some links are dead, because the target site, https://compass.cancerfighter.com, has closed.

Those dead links will be restored within weeks to a new website, namely http://pancreatic.altervista.org/posts.

The new website offers a tool for your research. It can be used to discover therapies using your keyboard's Ctrl F function.

For example, if you seek information on the PAXG regimen, press the Ctrl F keys, enter the keyword PAXG, then strike Enter. All text containing PAXG will be found.

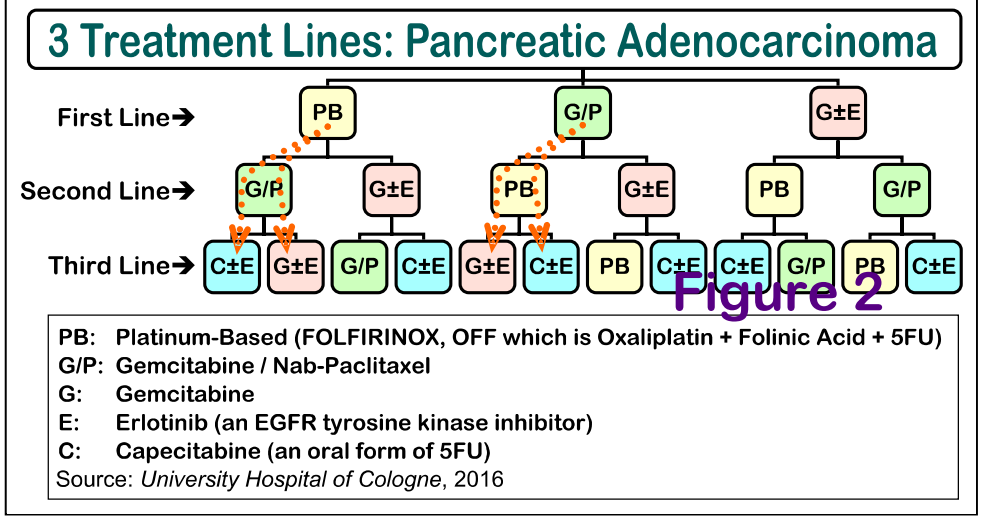


Figure 2

3rd Line Therapy

This Third Line Therapy section applies to all stages, Resectable through Metastatic. **Figure 1** and **ASCO** omit Third Line options.

The following regimens are viable options after Nab-Paclitaxel+Gemcitabine (NG) and FOLFIRINOX (FFX) have failed. Although it is good to avoid agents employed in earlier treatment Lines, some of these agents are nonetheless effective.

Future editions of this **Decision Guide** will rank chemo regimens by performance.

Beware: When the first two chemo regimens fail, too often uncreative medical oncologists run out of ideas, so they send patients to their colleague, the radiation oncologist. This referral doesn't benefit the patient, but merely spreads the wealth around.

The metastatic patient must never find himself in such a crisis.

Before BEGINNING his 1st Line Therapy the patient should already have found the best Clinical Trial or the best chemo regimen (discussed in the 1st Line metastatic section above) and the best 2nd line therapy. And, he should be prepared for 1st Line failures by monitoring CT and CA19-9, and thus should be ready to shift immediately to his well-researched 2nd Line Therapy.

Thus, the prospect of 3rd Line radiation should rarely arise. Radiation (a focal, non-systemic therapy) does NOT benefit metastatic patients, according to new research (see Abstract e16257). Systemic therapy is needed for a systemic disease.

- For Third Line chemotherapy consider LV5FU2 + NabP. LV5FU2 is an abbreviate 5FU/Leucovorin formulation called the *"de Gramont simplification."* According to their 2017 report, researchers from 15 French institutions found that the LV5FU2 + NabP regimen did as well or better then NabP+Gem (NG) in mostly therapy-naïve patients.

  Because LV5FU2 + NabP does not use some key components of First Line and Second Line regimens (such as Irinotecan, Gemcitabine and Oxaliplatin), the new regimen may also work well in heavily pre-treated patients (those for whom 1st Line and 2nd Line therapy have failed). Find a summary of the French research here and here.
- Low-toxicity SM-88's potential is described here. In early 2019 to finish its Phase 2 trial ECOG ≤2 patients were sought at 30 sites.
- Frail patients might consider Erlotinib combinations: Either G±E or the weaker C±E; see **Figure 2**, above. These regimens may be suitable AFTER 2nd line NabP+Gem or mFOLFIRINOX. Erlotinib is active only if a rash develops; see reports one, two & three.
  - ▶ In a 2016 German report a Gemcitabine combination is used in two sequential treatment lines with some success. And, the authors rely frequently on Erlotinib for part of a Third Line Therapy, although other targeted therapies, like Refametinib, might also be paired with Gemcitabine or Capecitabine (see **Figure 2**, above). G±E and C±E dosages appear in this 2017 guide.
  - ▶ In one path (G/P, then G±E, then C±E) Oxaliplatin might be added to G±E for more impact. Cisplatin might be added to G/P in at least two treatment paths (path G/P, then G±E, then C±E and path G±E, then G/P, then C±E). For hydration see Wrong IV Bag.
  - ▶ G±E performs nearly as well as FOLFIRINOX, if a rash develops during the first 4 treatment weeks. See this 2018 report.
  - ▶ This document alleges good performance for G±E and C±E, especially G±E if Bevacizumab is added, yielding G±E+B.
- This 2014 research report, issued by three Canadian institutions, asserts that PEFG is nearly as effective as FOLFIRINOX. PEFG is Cisplatin (Platinum) + Epirubicin + 5FU + Gemcitabine. Cisplatin requires hydration. Study the post: Wrong IV Bag.
- Another possibility is Nanoliposomal Irinotecan (MM-398) + 5FU (or substitute Capecitabine, 5FU's oral form), described here.
- BRCA-defect patients, 17% of cases, might consider Rucaparib, which performs modestly, but better as 2nd Line monotherapy.
- The OXIRI and AGAP Regimens are described here. To lessen the physical toll of IRI (Irinotecan) on the patient, OXIRI could be modified to OX (Oxaliplatin) + MM-398, where MM-398 (a micro-encapsulated form of IRI) can penetrate well at lower doses.
- NabP+Gem might be used a second time, if NabP+Gem was the 1st line therapy. Abstract P-147 here confirms effectiveness.
- NabP+Gem Upgrades are described here. And the new PAXG regimen offers possibilities. Download the report here.
- The GTX regimen (Gemzar® Gemcitabine, Taxotere® Docetaxel, Xeloda® Capecitabine) performs well, according to this 2017 trial report and to this 2019 abstract. This 2017 guide gives component dosages. Add Cisplatin, and the acronym becomes GTX-C.
- 3rd Line regimens may be gleaned from this fine 2014 article. Finding such salvage regimens vexes even oncology leaders.
- If Stage 4 patients achieve down-staging to 3, 2 or 1, the 2nd Line surgical steps above (including IRE) would be sought.

Notes

Preface to Notes

Preface For Resectable & Metastatic Disease

Generally, FOLFIRINOX (FFX) and NabP+Gem (NG) have been the more successful regimens. But, for the initial "induction" regimen which one is better and why? Refer to **Figure 3**.

In a 2019 **Seminars in Oncology** article Chinese researchers make several brilliant observations based on their re-examinations of data from 7 landmark clinical trials.

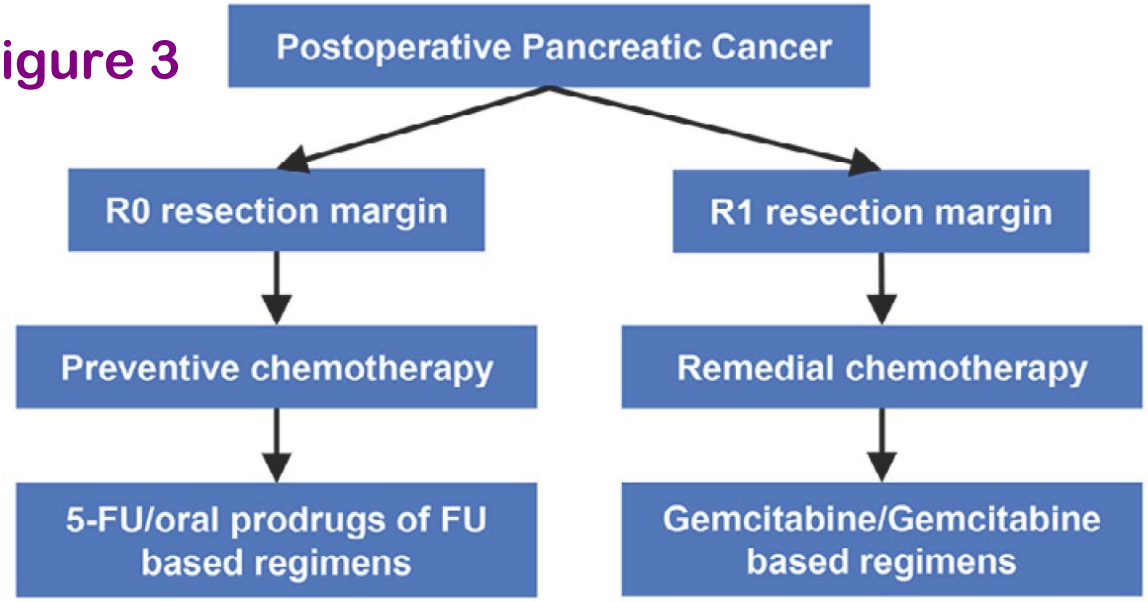
Their insightful observations are:

- When surgical resections achieve *"a negative margin (R0) [patients] benefit more from . . . fluorouracil-based adjuvant therapy"* (FFX). *"Gemcitabine-based regimens may be more effective . . . with [an inferior] positive resection margin (R1)."* The term *"margin"* is well defined in the report.

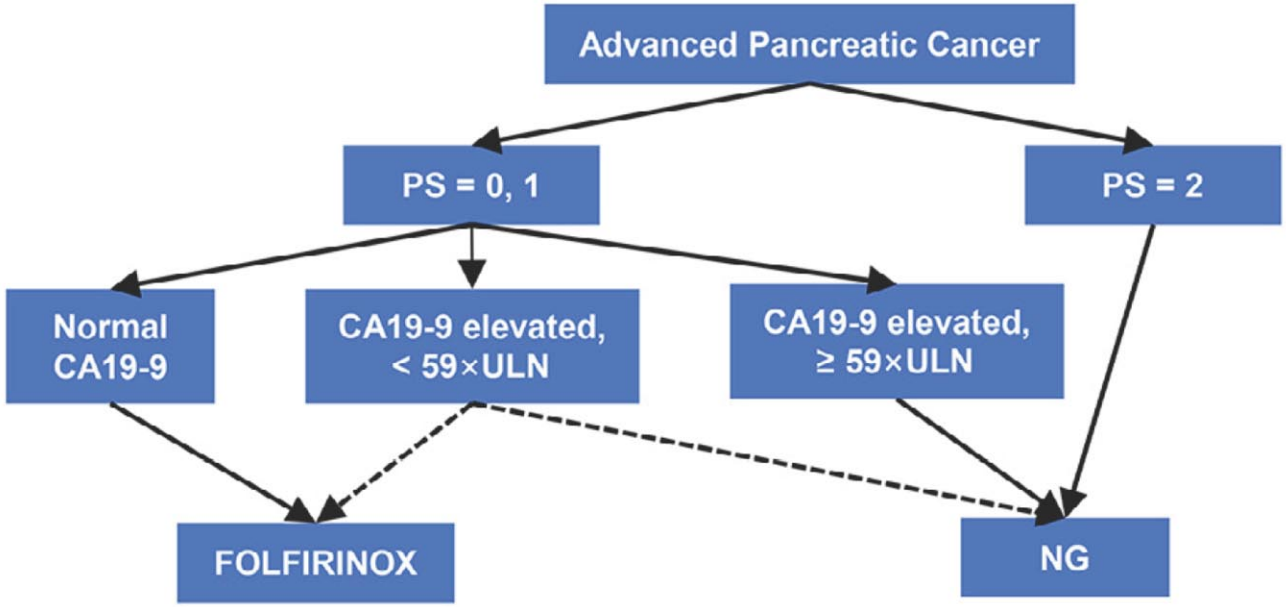
  Consider Neoadjuvant Therapy, if the patient is resectable at diagnosis.
- In non-surgery, metastatic cases *"NG may be more suitable for patients with . . . a high CA19-9 level after consideration of their performance status* [PS]*."*

Figure 3 depicts the decision tree, which appears in the 2019 report. Such algorithms are based on statistical probability. So, there will be cases in which the algorithm is faulty. Yet, generally, the decisions will be correct. PS (Performance Status) is defined here.

Figure 3



Selecting Adjuvant Chemotherapy for Resected Pancreatic Cancer



Selecting Chemotherapy for Advanced Pancreatic Cancer

Note 1

Note 1: Applies to All Disease Stages

- Hit Hard and Hit Early. Wait too long and you may not be strong enough later to endure the better therapies.
- Ensure that anti-obstruction stents are removable to allow IRE later. In addition, study and adopt all **Care Management** practices.
- Without fail observe the "Many Irons In The Fire" imperative. It is the difference between Life and Death.
- While awaiting diagnosis, identify good clinical trials, but only those having backbone therapies. Be sure the experimental agent or regimen has good performance numbers (Response Rate, Progression Free Survival, Overall Survival) based on past human trial phases. Non-human research is irrelevant. Most human trials have failed, but each began with successful non-human research.
  - ▶ Rapid trial research is critical, because often (not always) only therapy naïve patients are eligible for clinical trials.
- If insurance can be changed BEFORE diagnosis, do so. Avoid managed plans (including Medicare Advantage) – they limit access to the highest-rated cancer centers. Get Original Medicare plus Medigap plan F or G. The Medigap puzzle is addressed here.
- The NCCN Guidelines are highly informative. The family Care Manager must study them in the manner suggested here.
- 70% of patients acquire their treating oncologist via referral; they unwisely fail to research and select the physician themselves.
  - ▶ Except for key IRE facilities, seek care at "high-volume" centers. That is where your physician would seek care for himself.
  - ▶ Resectability is greatly dependent upon surgeon skill and facility competence. Travel is inconvenient, but death is more so.
  - ▶ Travel and lodging and other help are available, and major cancer centers typically arrange low hotel rates and free shuttles.
- Get genetic testing, certainly for BRCA, DDR, MSI, dMMR & Lynch Syndrome.
- Regimen NabP/Gem is enhanced if Gem is administered 24hrs after NabP, rather than same-day, according to this 2020 trial report.
- Test CA19-9 monthly. If little improved, rapidly explore the roles of Fungi and Bacteria described in this landmark USA research.
- Patients often suffer Pancreatic Exocrine Insufficiency (PEI) but are rarely treated via life-extending PERT, according to 2018 research.
- Be prepared to prevent body wasting far in advance. A weakened patient can't endure (and won't qualify for) the best therapy.
- Hospitalization is likely, so prepare for hospital threats. If an infection occurs, critical therapy will be delayed, perhaps a fatal delay.
- Elderly patients endure surgery as successfully as younger patients. From a review of 4,351 cases researchers found more postoperative complications, but no difference in length of hospital stay or postoperative mortality. Their Abstract e16227 affirms: *"Pancreatic resection . . . can be performed safely on elderly patients . . . in experienced centers by expert surgeons."*
- These 2019 articles describe Surgical Resection options, complications prevention and minimally-invasive techniques.
- Avoid blood transfusions; they have been found to be detrimental in pancreatic cases.
- Cancer Pain Management is detailed by an international handbook, by NCCN, by Johns Hopkins and by a Canadian guide.

Note 2

Note 2: Applies Only to Stages 1&2A, Resectable

- Anticipate failure of the first therapy. Immediately identify the next best therapy; make preparations with that therapy's provider.
  - ▶ Consider regimens and trials found among the Chemotherapy list, the Emerging Agents list and the Other Regimens list.
  - ▶ To obtain an Emerging Agent use a Clinical Trial, *Compassionate Use* or *Right To Try*.
- At the 1st CT, if there is no tumor reduction or if stable disease, elect surgical resection at once, assuming patient resectability.
- If the patient is no longer resectable, and if the 2nd CT shows no tumor reduction, shift immediately to the new pre-arranged therapy. Make the move rapidly within days; time is an enemy. Wait too long, and metastases will result. Likely, micro-metastases are already present. The patient can always return later to the first, low-performing regimen.
- If a Clinical Trial is sought, it must accept pre-treated patients, because the patient has already undergone a prior therapy. Some (not all) good ongoing trials are detailed in this Clinical Trials list, this Emerging Agents list and this Other Regimens list.
  - ▶ The patient's trial choice must be based on the performance numbers (Response Rate, Progression Free Survival, Overall Survival), numbers established by earlier human trial phases, not by animal studies.
  - ▶ To obtain an Emerging Agent use a Clinical Trial, *Compassionate Use* or *Right To Try*.

Note 3

Note 3: Applies Only to Stage 3, Borderline & Locally-Advanced

- If considered unresectable due to celiac blood vessel invasion, you might be resected by skilled surgeons employing the modified Appleby Procedure or by employing intraoperative IRE as part of standard resection. Both manage encased vessels and improve margins.
- Make immediate contact with one of the major IRE institutions, to learn whether IRE might achieve resectability. Even if IRE is suitable, the patient may benefit more by undergoing Neoadjuvant Therapy first. See also the Preface.
- Immediately identify suitable Clinical Trials using the recommended method. It is crucial to find the trial BEFORE any treatment is started, since trials are often (not always) limited to therapy-naïve patients. Otherwise, find one that accepts pre-treated patients
- At the 1st in-therapy CT, if there is no tumor reduction (even if the disease is stable), identify the next best therapy immediately. And, make arrangements with the future therapy's provider. But, delay switching therapies until the next CT.
  - ▶ Consider regimens and trials found among the Chemotherapy list, the Emerging Agents list and the Other Regimens list.
  - ▶ To obtain an Emerging Agent use a Clinical Trial, *Compassionate Use* or *Right To Try*.
- If the 2nd CT shows no tumor reduction, shift within days to the new prearranged therapy. Make the move rapidly; time is an enemy. Wait too long, and metastases will develop. Likely, micro-metastases are already present. The patient can always return later to the first, low-performing regimen.
- If a Clinical Trial is now sought, it must accept pre-treated patients, because the patient has already undergone a prior therapy. Some (not all) good ongoing trials are detailed in this Clinical Trials list, this Emerging Agents list and this Other Regimens list.
  - ▶ The patient's trial choice must be based on the performance numbers (Response Rate, Progression Free Survival, Overall Survival), numbers established by earlier human trial phases, not by animal studies.

Note 4

Note 4: Applies Only to Stage 4, Metastatic

- All will NOT be well if a typical backbone regimen is used. And, evidence suggests radiation will NOT help metastatic patients.
- Immediately seek a Clinical Trial using the recommended method. It is crucial to find the trial BEFORE any treatment is started, since trials are often (not always) limited to therapy-naïve patients. Otherwise, find one that accepts pre-treated patients.
  - ▶ Consider regimens and trials found among the Chemotherapy list, the Emerging Agents list and the Other Regimens list.
  - ▶ To obtain an Emerging Agent use a Clinical Trial, *Compassionate Use* or *Right To Try*.
- At the 1st in-therapy CT, if there is no tumor reduction (even if the disease is stable), identify the next best therapy immediately. And, make arrangements with the future therapy's provider. But, delay switching therapies until the next CT.
- If the 2nd CT shows no tumor reduction, shift within days to the new prearranged therapy. Make the move rapidly; time is an enemy. Wait too long, and metastases will develop. It is likely that micro-metastases are already present. The patient can always return later to the first, low-performing regimen.
- If a Clinical Trial is now sought, it must accept pre-treated patients, because the patient has already undergone a prior therapy.
  - ▶ Some (not all) good ongoing trials are detailed in this Clinical Trials list, this Emerging Agents list and this Other Regimens list.
  - ▶ The patient's trial choice must be based on the performance numbers (Response Rate, Progression Free Survival, Overall Survival), numbers established by earlier human trial phases, not by animal studies.
- A new paradigm is emerging: Metastases removal can be justified if there are ≤3 in one organ (liver or lung), according to innovative oncologists. The result: Reduced tumor and chemotherapy burden and increased survival. More details here.