

THIRD ANNUAL

*Update on the Management
of Gastrointestinal
Malignancies*

*October
20-22, 2006*

**Estancia La Jolla Hotel & Spa
LA JOLLA, CALIFORNIA**

Chairman:

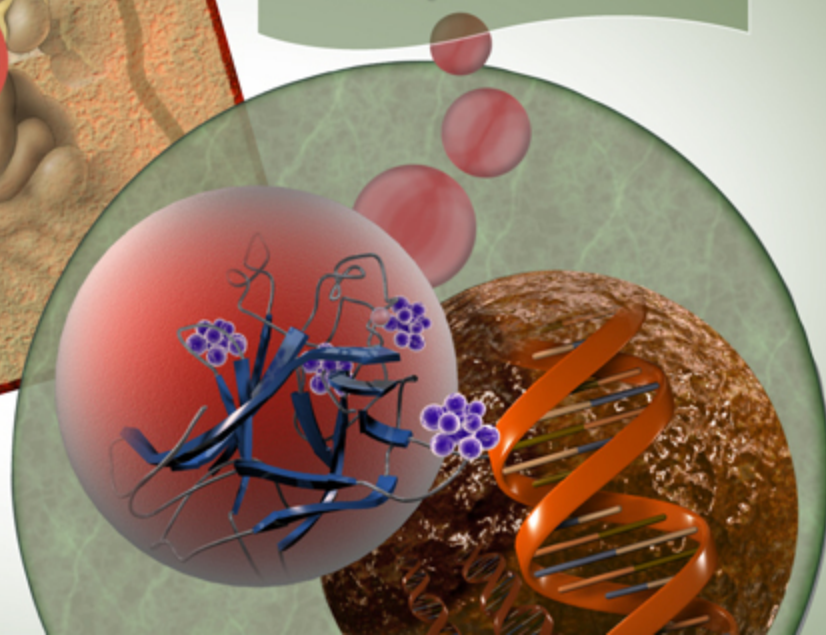
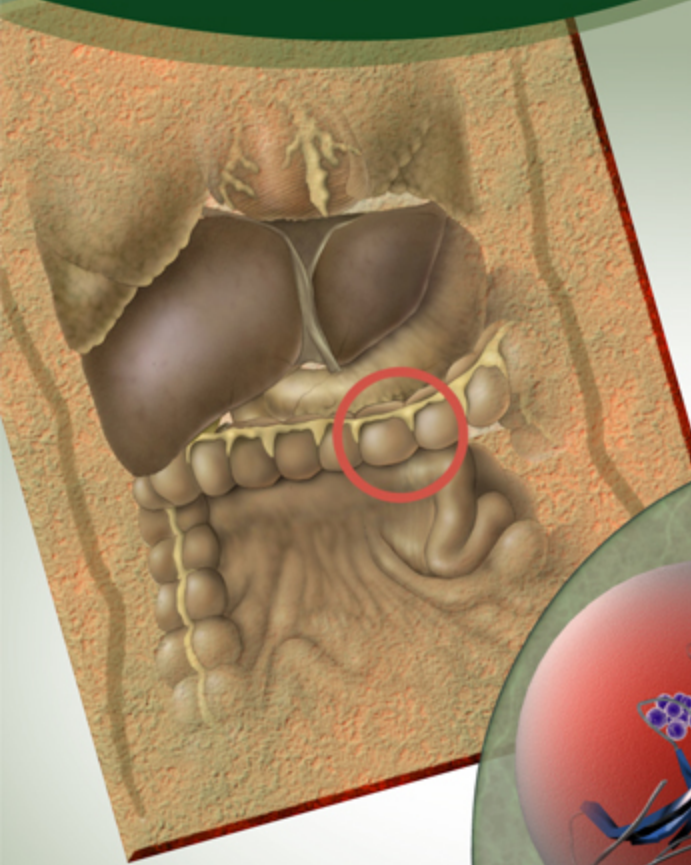
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Hepatobiliary Malignancies

Systemic Options

Hepatocellular Cancer

- 5th most common cancer worldwide
 - >650,000 cases worldwide
 - <20,000 cases in the US
- Multiple underlying etiologies
 - Hep B, Hep C
 - Aflatoxin
 - Chemical exposures: vinyl chloride
 - Other causes of cirrhosis:
 - Alcohol, hemochromatosis, alpha-1 antitrypsin deficiency, etc

HCC Treatment

- Local therapies
 - Surgery—near impossible in a cirrhotic liver
 - RF Ablation
 - Cryoablation
 - Alcohol Injection
 - Trans-arterial chemoembolization—doesn't clearly help people but we can do it
 - Liver Transplantation
 - Only local therapy that deals with the fact that there is a field defect
 - Only eligible with 1 tumor < 5 cm or 3 or fewer tumors, none more than 3 cm
 - 70% 5-year survival (is this “wasting” a liver when other indications have a 90% 5-year survival?)

Systemic Therapy of HCC: Issues

- HCC is not a single disease entity
 - Underlying etiology may play a role in disease biology
 - Highly variable disease course
- Most patients with HCC also have cirrhosis
 - Two high mortality diseases intertwined in 1 liver
 - Less predictable drug metabolism
 - Many present with poor PS
 - And even poorer liver function

Systemic Therapy Choices

- Chemotherapy
- Hormonal Therapy
- “Immune” Therapy (interferon)
- Targeted Therapy

Chemotherapy

- Doxorubicin
 - Arguably the most effective chemotherapy agent
 - Use is limited
 - Hepatically metabolized
 - Elevated bilirubin makes doxorubicin too toxic
 - Response rates vary (10-26%)
 - Meta-analysis and limited RCTs exist
 - Efficacy is questionable: survival (6-8 months for doxorubicin) does not differ that much from supportive care

Chemotherapy

- 5-FU (capecitabine)
 - The other “standard” drug
 - Safer in liver failure/cirrhosis
 - Ubiquitously metabolized
 - I could not find a randomized trial of 5-FU vs placebo

Combined Chemotherapy

- PIAF
 - Platinum, interferon, adriamycin (doxorubicin), 5-FU
 - In phase II trials had RRs approaching 40%
- Phase III trial in 188 patients: PIAF vs doxorubicin
 - RR was 20% vs 10%, respectively
 - Survivals were 8.7 vs 6.8 months (p, 0.83)
 - HR = 0.98

Other Chemotherapy Agents

- Platinums
 - Combined analyses show that they generally increase RR when added to other drugs
 - But no survival benefit has been seen by adding cisplatin to other chemo
- Irofulven
 - Single agent produces RR of 7-10%
 - Further work is in combination strategies
- T138067, T900607
 - In phase I trials at Hopkins (T138067) and Vanderbilt (T900607) had significant activity in a few HCC patients
 - In phase II, T138067 had some limited activity (RR < 10%)
- Thymitaq
 - Antifolate with “promise”
 - Phase III trial made doxorubicin look good

Hormonal Therapy

- Estrogen has been implicated in the etiology of HCC
- Estrogen receptors have been found on liver cells, benign hepatic lesions and hepatomas
- Tamoxifen, an antiestrogen (mostly), has had variable impact on RCTs

Tamoxifen Randomized trials

- 12 RCTs and 4 meta-analyses
 - 4 positive trials
 - 8 negative trials
 - 2 positive meta-analyses
 - 2 negative meta-analyses
- 2 largest trials were negative
 - Barbare, et al JCO 2005 (420 pts)
 - Suggested the subset with good hepatic function did get survival benefit
 - CLIP trial Lancet, 1998 (477 pts)
- My personal favorite
 - Tamoxifen vs TACE + tamoxifen
 - Survival was ~12 months for both arms

Other Hormonal Treatments

- Androgen receptors have also been found on HCC
 - Not as many randomized trials, but
 - All trials of anti-androgens (LHRH antagonists, flutamide) are negative
- Megesterol
 - Apparently progesterone receptors also exist
 - One phase II looked promising
 - I'm unaware of any phase III trials, but it makes people hungry

Somatostatin Analogues

- Rationale:
 - HCC cells have demonstrated somatostatin receptors
 - Somatostatin can inhibit growth of cells in vitro
- Results of trials
 - RCTs have had conflicting results in terms of survival
 - May have some QOL benefit that needs further exploration

Interferon

- This has intriguing issues
 - Interferons have anti-tumor activity, though limited
 - Interferon also has anti-HCV and anti-HBV properties
- In RCTs
 - In HBV patients there was survival benefit
 - In HCV patients there was no survival benefit
 - Were the diseases different or is this an effect of small trials?

Standard Therapy Conclusions

- There is probably some limited activity from many of the old therapies
 - Chemo: doxorubicin and 5-FU
 - Hormones: tamoxifen, octreotide
 - Immune therapy: interferon
- However, these agents each work with a subset of patients and we have not spent any effort dissecting this issue out

Can targeted therapies save
the day?

Angiogenesis

- HCC is highly vascular
- HCC overexpresses VEGF (and this may confer a poor prognosis)
- HCC may have VEGF receptors itself
- In pre-clinical trials
 - VEGF inhibitors have inhibited HCC growth
 - PTK 787 inhibited both angiogenesis and inhibited tumor growth through an angiogenesis-independent effect

Angiogenesis in HCC

- Clinically some hints of activity
 - Bevacizumab has had ~10% responses in a couple of phase II trials (2 of 25 pts in 1 study)
 - TSU-68 (inhibits VEGFr, PDGFr and FGFr) produced response in 1 of 15 pts
 - Thalidomide, which is a questionable angiogenesis inhibitor has had variable, mostly minimal effects
 - Didn't stop Celgene from promoting its use
 - Best study had 38 pts, 5% RR and showed poor tolerance

EGFr

- Overexpressed in a variety of tumor types including HCC
 - Response rate to erlotinib <10%
 - Response rate to lapatinib <10%
 - Response rate to cetuximab 0%
- In other words, relatively poor, but about the same as everything else

NF Kappa B

- NF Kappa B is activated in most forms of liver injury
 - Both Hep B and Hep C induced HCC may have origins in NF kappa B activation
 - There are no pure NF kappa B inhibitors in testing now, but
 - Bortezomib inhibits proteasome degradation of I kappa B, the inhibitor of NF kappa B
 - Bortezomib was more active than doxorubicin in F4 HCC models
 - And additive with doxorubicin in HCC while synergistic in lymphoma

NF kappa B

- Bortezomib single agent in 20 German pts produced 7 stable diseases
- 2nd study is ongoing at Mayo clinic
- Bortezomib + doxorubicin is being studied in HCC in ECOG
 - Correlatives in serum should help us better understand how this works

Other Targets

- Src
 - Overexpressed in a variety of tumors including HCC
- Cox-2
 - Overexpressed in up to 80% of HCC and inhibition works in the lab
- M-TOR
 - Downstream from EGFR
- Myc
- Cyclin dependent kinases

HCC Conclusions

- Chemotherapy and other systemic therapies have had limited efficacy
 - We need to better understand in whom they can help
 - Does the underlying etiology of the cancer predict more for efficacy of some of these agents?
 - For now, systemic therapy should mostly be done on clinical trials
- Targeted therapies have thus far met with limited success, but
 - If we figure out how to combine these agents better we may be able to come up with more effective regimens

Biliary Tract Cancer

Background

- Epidemiologic data is poor
 - US lists 8,570 cases and 3,260 deaths of gallbladder and other biliary (extrahepatic) for 2006
 - US can't seem to separate intrahepatic cholangiocarcinoma from HCC
 - Worldwide, there is geographic variation
 - South American populations have highest incidence (up to 13/100,000) (US = 1.8/100,000)
 - Some European countries, such as Hungary, Poland and Germany have higher incidences (9.2-6.8/100,000)
 - Asia varies:
 - Japan 11.9/100,000 (1999 data)
 - India has been as low as 1/100,000 but is on the rise, particularly in Delhi where female incidence of 8.9/100,000 has been reported
 - Female:male ratio is 2.5-3.0/1

Reasons for confusion

- Heterogeneous disease
 - Intrahepatic cholangiocarcinoma
 - Extrahepatic biliary tract carcinoma
 - Includes Klatskin tumors
 - Gallbladder carcinoma
 - ?periampullary carcinoma
 - Probably a major source for adenocarcinoma of unknown primary

 - Not all are included in each country's stats, particularly US which puts intrahepatic cholangiocarcinoma with HCC because we let the federal government do this.

What do we have?

- Chemotherapy
 - 5-FU (without it no GI cancer talk is complete)
 - Gemcitabine
 - Oxaliplatin
 - Other platinumums
- Un-chemotherapy agents
 - EGFR inhibitors
 - Bevacizumab

5-Fluorouracil

- No GI cancer talk can proceed without paying homage to 5-FU
 - Response rates for single agent or multi-agent 5-FU regimens range from 0-36%
 - Median survival is usually ~ 6 months
 - No benefit has been clearly demonstrated for adding any of the older therapies to 5-FU

Gemcitabine

Reference	Schedule	# of patients	Response Rate	TTP	Overall Survival
Penz, et al	2200/m2 Q o week	32	22%	5.6 mos	11.5 mos
Valencak, et al	1200/m2 Qw x3	24	4%	3.5 mos	6.8 mos
Kubicka, et al	1000/m2 qw x3	23	30%	4.4 mos	N/A
Arroyo, et al	1000/m2 qw x3	39	36%	N/A	6.5 mos

These and other trials are all summarized in Scheitauer W, Semin Oncol 29:6 (suppl 20), 40-45, 2002

Gemcitabine + 5-FU

Reference	Gemcitabine + _____	# of pts	Response Rate	TTP or PFS	Overall Survival
Murad (Am J Clin Oncol 26: 151-4, 2003)	Bolus 5-FU	9 pts	33%	TTP	9 months
Jacobson D ASCO 2003	Bolus 5-FU with LV	42 pts	9.5%	3.8 months	6.8 months
Hsu C, et al ASCO 2003	Bolus 5-FU	26 pts	19%	4.2 months	7.3 months
Knox J, et al GI Symposium, 2004	Capecitabine	35 pts	26%	6.8 months	10.3 months

2nd study of gem-cape in 57 pts, RR 18%, OS 7 months

Oxaliplatin

- Never evaluated as a single-agent
 - In combination studies:
 - 5-FU/LV: RR 19%, OS 9.5 months (Nehls, et al. Br J Cancer 87: 702-4, 2002)
 - Capecitabine: RR 23%, OS not reached (Nehls, et al. ASCO 2003)
 - Gemcitabine, 1st line, normal bili: RR 36%, OS 14.3 months, Maindrault-Goebel F, et al ASCO, abstract 1178, 2003
 - Gemcitabine, 2nd-3rd line, abnormal bili: RR 22%, OS 7.6 months, Maindrault-Goebel F, et al ASCO, abstract 1178, 2003

Gemcitabine + other platinumums

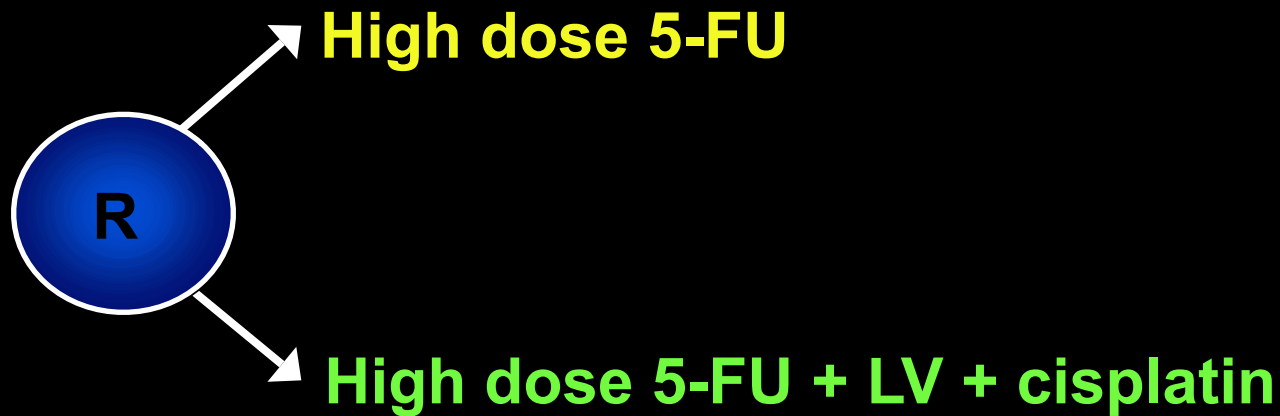
Reference	Type of platinum	# of pts	RR	Survival
Thengprasert, et al GI ASCO	Cisplatin	24	33%	13 mos
Reyes-Vidal, et al GI ASCO (GOCCHI trial)	Cisplatin	42	48%	7 mos
ASCO 2003	Carboplatin	13	30%	N/A

In a pooled analysis of 88 clinical trials in biliary tract cancer, RR for gem was in the 20% range, but this doubled with the addition of Cisplatin (same occurred with 5-FU) Eckel, et al ASCO 2006

Chemotherapy Conclusions

- Chemotherapy works some
 - Response rates vary from study to study
 - Either gemcitabine or 5-FU may be considered a standard single-agent option
 - Single agent may be just as effective as couplets, although overall it appears platinumums at least add to the RR for gem or 5-FU
 - However, no new agents are being developed that will really change the natural history of this disease

EORTC 40955: Study Design



Targeted Agents

- Erlotinib
 - 6% RR in 35 patients
 - 25% progression-free at 6 months
- Lapatinib
 - Combined HER-1/HER-2 antagonist
 - Has activity in breast cancer
 - Has nothing in biliary tract cancer

Future Directions of Systemic Therapy

Gemcitabine + oxaliplatin needs to be evaluated further

- Vanderbilt is planning a gem-ox + pulsed erlotinib trial
- Cooperative groups need to move towards randomized trials
 - To establish a standard
 - Move forward with new agents
- Please don't tell anybody, but there are actually many targeted agents that don't block VEGF or EGFR that have potential
 - Pre-clinical data shows HDAC inhibitors reasonably active and great when combined with gemcitabine (for example)

Radiation Therapy

- Observations from phase II trials suggest that local control can be achieved.
 - Improved local control may be achieved with
 - Brachytherapy-catheter can be placed at surgery
 - IORT—no data that it improves survival after resection
 - Cameron, et al suggested improved survival when brachytherapy was used after biliary stent placement in the palliative setting
 - Multiple phase II trials in the palliative care setting suggest survivals for EBRT of 9-13 months

Chemoradiation

- No randomized trials of chemoradiation vs radiation alone
 - However, in every disease where it has been tested chemoradiation has been better
 - The majority of studies and analyses have used 5-FU and radiation
 - Response rates may be improved
 - Survivals may be improved, but not proven
 - All the above are data for locally advanced disease, not for metastatic disease

Biliary Tract Conclusions

- Chemotherapy in the metastatic setting has some effect
 - Response
 - In one small trial, survival
 - In the same trial, QOL maintenance
- Radiation
 - Probably best when given with chemotherapy
 - Probably palliates in the locally advanced setting
- Chemoradiation
 - Warrants further investigation in locally advanced and possibly adjuvant settings

Future Directions in biliary Tract Cancer

- We need to learn more about this set of diseases
 - We know little about genetic changes compared to other diseases
 - Melanie Thomas presented data from MDACC database/tissue bank showing HER1 as relevant to biliary tract cancer at ASCO 2006
 - Immediately after her presentation, Ramesh Raminathan presented the lack of efficacy of lapatinib
 - We know little of the subtypes of the disease (I am a lump-er as well, but it might not always be perfect)
 - One analysis of cell cycle regulatory proteins showed that differences existed between subtypes and differences in some cell cycle regulatory proteins were prognostic

The Chair would like to thank the following companies for their generous support of this CME activity.

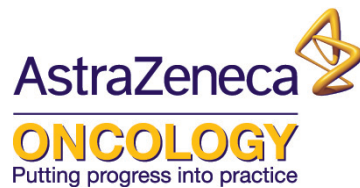


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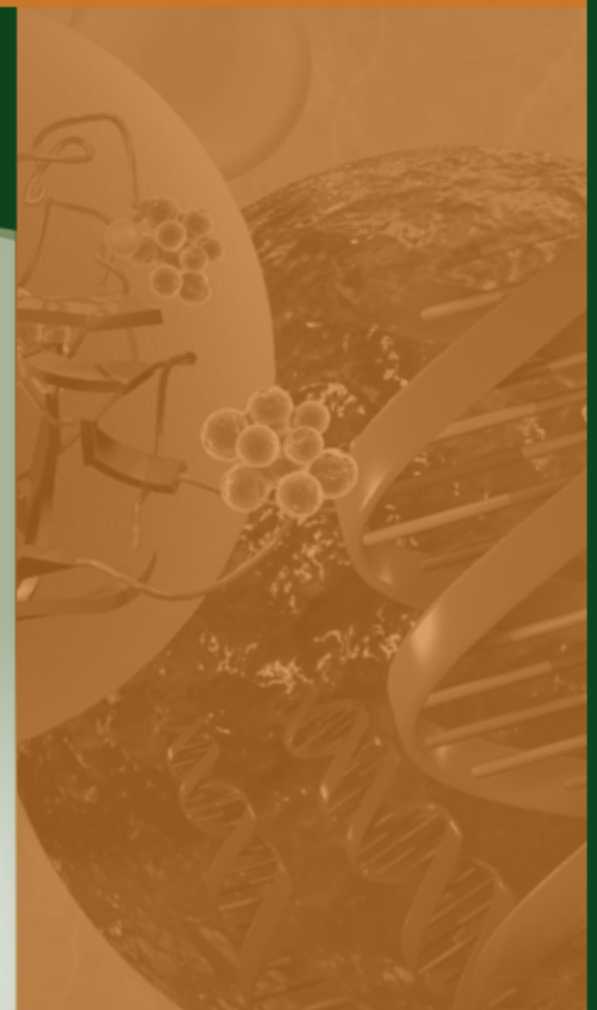
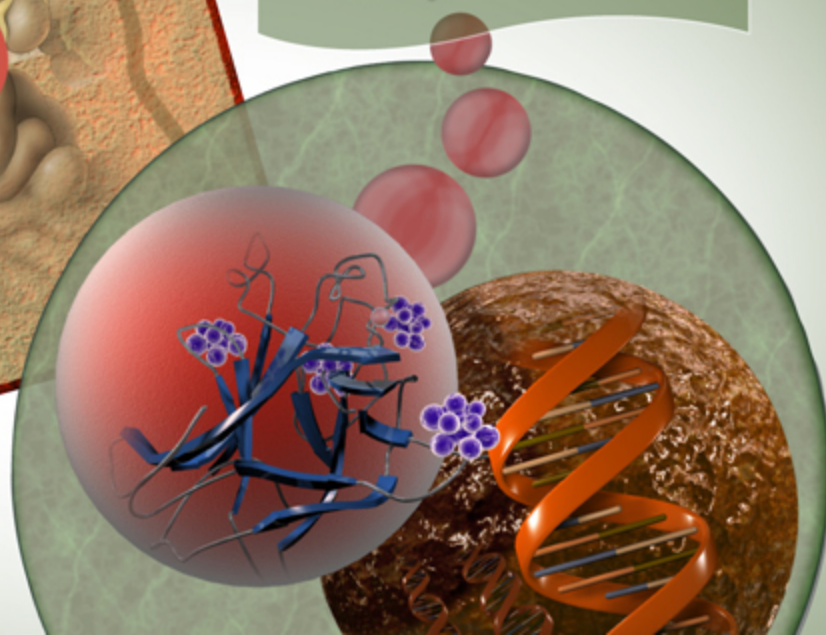
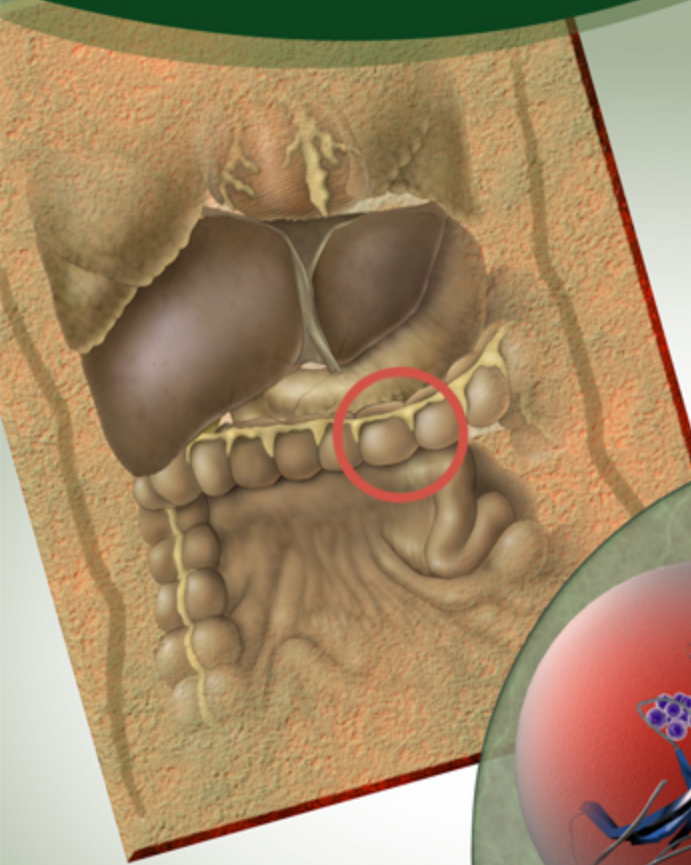
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