HYPOFRACTIONATION IN GASTROINTESTINAL MALIGNANCIES -A BRIEF OVERVIEW

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- Hypofractionation had been used since 1930s but was abandoned later.
- Reappeared in 1970 s.
- Historically, radiation treatment of GI malignancies involved 5 – 6 weeks of low dose per fraction of RT.
- Hypofractionated RT over 1-4 weeks is an emerging alternative in curative setting.
- Hypofractionation is regularly used in palliation of all GI cancers.

- 1970s and 1980s experiments in US aimed at reducing late effects by increasing number of fractions
- Recent trend in fractionation is to increase dose per fractions much larger than 2 Gy for curative radiotherapy
- SRS and SBRT are methods of extreme hypofractionation with good results for lung and brain
- They have good tumour control with less effect on normal tissues
- In the case of SABR , local control rates are very high with small sized tumours and it decreases with increase in tumour size

- In a study conducted by Brown and colleagues quoted that tumour control probability is a simple function of BED regardless of fractionation regimen
- High TCP in large BED
- This explains the success of SRS and SBRT
- Hypofractionation is effective in tumours with low α/β values

Eg: Ca prostate, Ca breast

- α/β value for GI tract is usually high and hence the use of hypofractionation in GI malignancy was questionable

Hypofractionation in curative setting

Oesophagus

- Preop CCRT (CROSS trial]
- Phase 3 study
- Surgery +Neoadjuvant chemo RT VS Surgery alone
- 41.4 GY in 23# with concurrent carboplatin and paclitaxel.
- Median OS was 48.6 months VS 24 months[Neoadj arm Vs Surgery alone]
- Median OS for squamous was 81.6 months VS 43.2 months for adeno carcinoma
- PCR rate of 23% in Adenocarcinoma and 49% in Squamous cell carcinoma.

Gastric cancer

- Role of RT in non metastatic gastric cancer is controversial
- Hypofractionated radiotherapy are mainly used for palliation
- 36Gy/12# and 20Gy/5# are found to be effective and well tolerated

Pancreatic cancer

- Role of RT in curative aspect of pancreatic RT is controversial
- RT increases the rate of R0 resection
- Conventional fractionation is used in all landmark studies (UKCCR ACT1 trial, EORTC trial)
- Hypofractionated RT was evaluated with upfront surgery in PREOPANC trial

PREOPANC trial

- Multicentric phase 3 trial
- Borderline resectable ca pancreas- 246 patients
- Neoadjuvant chemoradiation- 36 Gy/15# with concurrent gemcitabine Vs primary surgery followed by adjuvant gemcitabine
- Difference in median survival was 1.4 months
- 5yr overall survival- 20.5% in neoadjuvant group vs 6.5% in upfront surgery
- Supports the use of hypofractionated RT in pancreas

SBRT in ca pancreas

- Indicated in
  - Borderline resectable tumours
  - Unresectable tumours and resected tumours with positive margins
- Dose- 18- 36Gy/3#

Table 2
Stereotactic body radiation therapy for locally advanced pancreatic cancer.

			specified)			
Koong et al.[16]	15	15, 20, or 25 Gy × 1	0	100%	11	5
Koong et al.[17]	19	45 Gy IMRT followed by 25 Gy × 1 boost	2 (12.5%)	94%	8.3	6
Hoyer et al.[18]	22	15Gy × 3	79% acute grade 2+	57%	5.4	Not available
Schellenberg et al.[19]	16	25 Gy × 1 after induction gemcitabine + post-SBRT gemcitabine	1 (6%) acute 2 (13%) late	100%	11.4	9.1 for all patients; 22.3 for living patients
Schellenberg et al.[20]	20	25 Gy × 1 after induction gemcitabine + post-SBRT gemcitabine	0 acute 1 (5%) late	94%	11.8	4.3
Herman et al.[21]	49	6.6 Gy × 5 after induction gemcitabine	1 (2%) acute 3 (6%) late	78%	13.9	13.9
Mahadevan et al.[24]	36	8, 10, or 12 Gy × 3 followed by adjuvant gemcitabine	5 (14%)	78%	14.3	24
Mahadevan et al.[25]	39	8–12 Gy × 3 after induction gemcitabine	0 acute 3 (9%) late	85%	20	21
Gurka et al.[26]	10	5 Gy × 5 with concurrent gemcitabine	0	40%	12.2	Not available
Polistina et al.[28]	23	10 Gy × 3 with induction and concurrent gemcitabine, ± surgery, ± maintenance chemotherapy	0	82.6%	10.6	9

Based on these considerations, MSKCC is currently leading a dose escalation trial to evaluate the safety and feasibility of SBRT delivered in three fractions for patients with LAPC who have received induction FOLFIRINOX or gemcitabine/Abraxane chemotherapy. The primary objective is to determine the maximum tolerated dose of three-fraction SBRT starting at 9 Gy for patients with LAPC after 4 months of induction chemotherapy.

Hepatocellular carcinoma/ Cholangiocarcinoma

- Role of RT in liver tumour is limited due to greater RILD risk
- So volume of normal liver irradiated to be reduced
- With advances in image guides radiation therapy techniques extreme hypofractionated SABR is being used in HCC.
- SBRT is also used as the initial treatment for HCC with extensive portal vein tumour thrombus originally unsuitable for TACE or resection .This cause adequate tumour shrinkage and portal vein flow restoration.Pts could undergo further treatments such as resection or TACE.

RTOG 1112

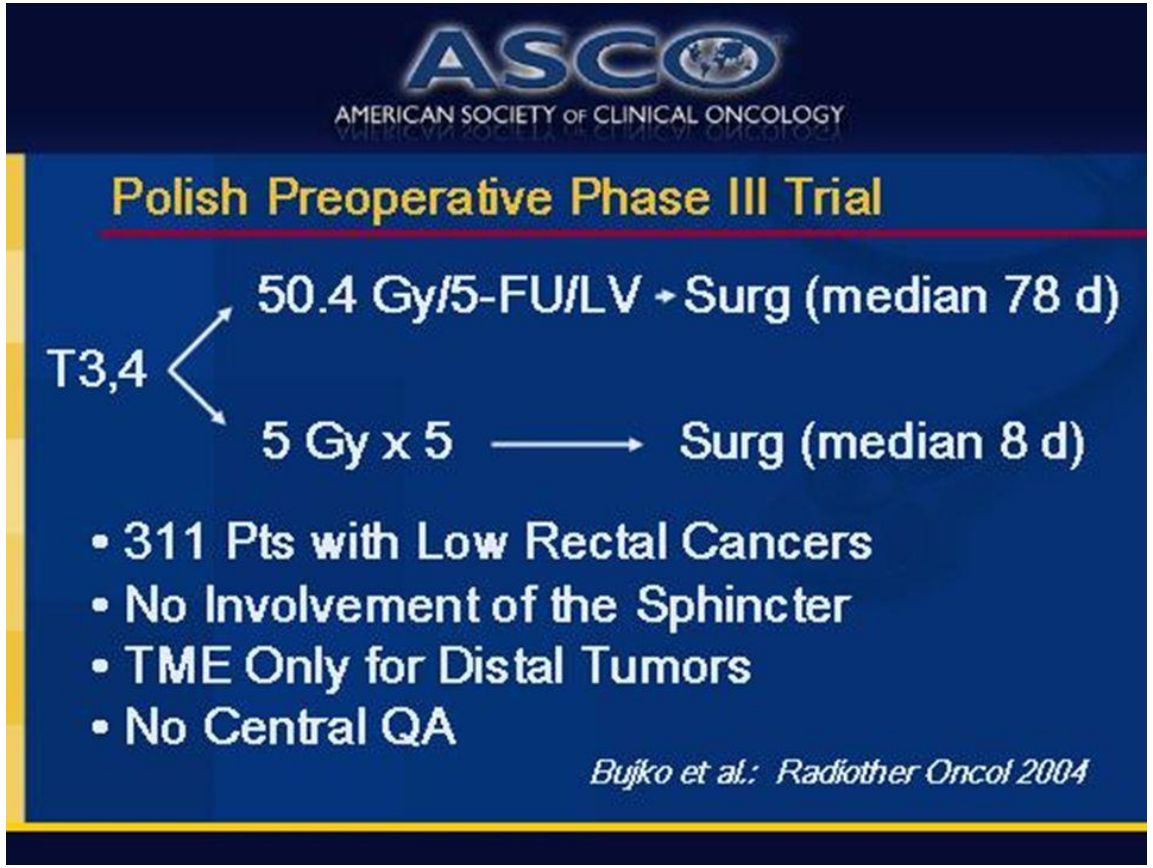
- Phase 3 Study in HCC
- Pts unsuitable for resection,TACE,transplant,ablation with PS 0-2.
- Sorafenib VS SBRT followed by adjuvant sorafenib in HCC
- 193 patients
- RT dose- 27.5- 50Gy/5#
- Endpoints- OS and PFS
- Conclusion- OS [12.3 months VS 15.8 months and median PFS improved with SBRT[5.5 months to 9.2 months] with no significant increase in adverse events.

- SBRT has been used in oligometastatic liver mets.
- NRG-RTOG BR001 trial- SBRT to 2-4 sites in oligometastatic ECOG 0-2 pts found no dose limiting toxicity for 1# every 2nd day.45 Gy in 3# in liver.
- SBRT as palliation in main portal vein tumour thrombosis.
- SBRT used as bridging therapy or downstaging prior to transplantation.

Rectal carcinoma

- Eventhough Pre op longcourse CCRT was the standard of care in rectal cancer (German rectal cancer trial- 2004)
- Short course preop RT- 25Gy/5# was standard approach in parts of Europe and Australia since 1997 (Swedish rectal cancer trial) which showed that short course RT has significantly reduced local recurrence and cancer specific survival,BUT this was before TME era.
- Depicts the role of hypofractionation in ca rectum
- Can be explained by α/β of rectal wall being 3.5

Polish rectal cancer trial



Polish Trial

- Polish Study (Br J Surg. 2006): 316 patients with resectable T3-4 rectal cancer, no sphincter involvement, tumor palpable on DRE (1999-2002).

	Preop short course RT	Preop conventional RT
5 y. OS	67.2%	66.2%
5 y. local relapse	9.0%	14.2%
DFS	58.4%	55.6%

NO difference in anorectal or sexual dysfunction

TROG 01.04 trial

- T3N0-2M0 rectal cancer 12cm from anal verge- 163 patients each
- 25Gy/5# with early surgery and adjuvant chemotherapy with 6 cycles of 5FU+CALV VS 50.4Gy/28# with concurrent infusional 5FU and surgery in 4- 6 weeks and 4 cycles of adj chemo with 5FU +CA LV

	Short course	Long course	HR
5yr Distant recurrence rate	27%	30%	1.04
5yr Overall survival	74%	70%	1.12
Late toxicities	5.8%	8.2%	P= .53

- Both trials showed high rates of early radiation toxicity in long course group than short course group.

- NO difference in distant recurrence, RFS, OS or late toxicity.

Stockholm 3 Trial

- 5x5 Gy -> surgery within 1 wk

  vs

- 5x5 Gy -> surgery after 4-8 wks

  vs

- 50 Gy-> surgery after 4-8 wks

Outcome- Median time to local recurrence

- Short course early surgery group 33.4 months.
- Short course late surgery 19.3 months.
- Long course RT 33.3.months.

- Acute RT toxicity was reported in less than 1% after SCRT with early surgery VS 7% after delayed surgery VS 5% after long course RT.
- Post op complications were similar in both arms.
- Between SCRT regimens,delayed surgery arm did show lesser post op complications.
- PCR rates 12.5% in SCRT delayed and long course RT and 0.8% in SCRT early surgery arm.
- Acute toxicity was more in delayed SCRT arm.[grade 3 toxicity is 7%] and 1% in early surgery arm.

Anal cancer

- Conventionally fractionated definitive CCRT is the standard of care (UKCCCR ACT1 trial, EORTC trial,RTOG 87-04
- 3 ongoing clinical trials ,UK ACT3,ACT4 and US DECREASE trials are evaluating the strategy of dose de escalation in T1-2 squamous cell carcinoma anal canal.

- Palliative RT in anal canal is hypofractionated- 20Gy/5# or 25Gy/5#
- Further investigation needed in hypofractionated RT in anal cancers

Hypofractionation and COVID pandemic

- Period of evidence based medicine vs opportunity
- Increased use of short course RT in ca rectum due to constraints
- Many publications were there which recommended COVID- 19 adapted dose fractionations to reduce patient exposures and optimise use of limited resourses.
- Many recommendations in the era of COVID -19 US and EUROPE adopted many hypofractionated regimens.
- The need to establish and disseminate an evidence base around this phenomenon is there.

Hypo fractionation in palliative setting

- Oesophagus,Stomach, Pancreas, Rectum, Anal canal-20 Gy in 5#,30
- Gy in 10# commonly used regimens.
- Hemetemesis- 8Gy single #
- Malena-8 Gy single #
- Bleeding per rectum -8 Gy single#

Sites	Radical	Palliative
Esophagus	40Gy/15# 50Gy/16-20#	30Gy/10# 20Gy/5#
Stomach	-	6-8Gy/1#
Liver	16-30Gy/1-3# 48-60Gy/3-5#	-
Cholangiocarcinoma	67.5Gy/15# 60Gy/3-6#	-
Pancreas	30-33Gy/5#	30-40Gy/5# 20Gy/5# 30Gy/10#
Rectum	25Gy/5#	-

Hypofractionated radiotherapy and augmentation of immune response

- ASCO published protocol of an ongoing phase 2 trial
- Augmentation of immunotherapy in metastatic GI malignancy by hypofractionated RT (ARM-GI) in patients progressing on immunotherapy.
- By Hewitt Chang, Lucia Andemicael, Moshiur Mekhail et al
- Phase 2 single arm study conducted for patients with metastatic GI tumours with atleast 2 mets,one of which can be left unirradiated.
- 30Gy/5# IMRT/SBRT given to symptomatic sites and continuation of immunotherapy.
- To assess ORR, PFS,OS, local control at irradiated and unirradiated sites,incidence of new metastatic lesion and time to new systemic therapy.

Background

- Palliative hypofractionated RT helps in symptomatic relief and distant effect by abscopal effect
- Increase tumour immunogenicity, tumour microenvironment modulation and immune cell recruitment
- May lead to relieve symptoms,increase the immunr response,delay next line systemic treatment and improvement in unirradiated sites.

THANK YOU