

UPDATES IN THE MANAGEMENT OF GASTROINTESTINAL STROMAL TUMORS (GISTs)

Essay

*Submitted for partial fulfillment of Master Degree in General
Surgery*

By

Wadie Boshra Gerges

(M.B.B.Ch)

Under Supervision of

Prof. Awad Hassan Alkayal

Professor of General Surgery

Faculty of Medicine–Ain Shams University

Dr. Gamal Fawzy Samaan

Lecturer of General Surgery

Faculty of Medicine–Ain Shams University

Faculty of Medicine

Ain Shams University

2011

List of Contents

Title	Page
○ List of Figures	i
○ List of Tables	iv
○ List of Abbreviations	v
● Introduction & Aim of the work	1
● Historical background	4
● Pathology of Gastrointestinal stromal tumors	7
A) Epidemiology	7
B) Cells of Origin (Interstitial cells of Cajal)	9
C) Etiology & Risk Factors	10
D) Pathological features	11
1) Gross Pathology	11
2) Histopathological features of GISTs	14
E) Classification & Grading	25
F) Prognostic Factors & Risk Assessment	26
G) GIST Pathogenesis	31
H) Immunohistochemical Features of GISTs	40
I) Differential Diagnosis of GISTs	48
● Diagnosis of Gastrointestinal stromal tumors	57
A) Clinical features of GISTs	59
B) Investigations for GISTs	62
1) Blood tests	63
2) Endoscopy	64
3) Ultrasonography	65
4) Endoscopic ultrasound (EUS)	66
5) Biopsy	68
6) Conventional barium studies	70
7) Computed Tomography (CT) of the Abdomen ...	72
8) Magnetic Resonance Imaging (MRI)	78
9) Positron emission tomography (PET)	80
10) Angiography	83
11) Plain radiography	85

List of Contents

Title	Page
• Treatment of Gastrointestinal stromal tumors	86
A) Introduction	86
B) Management of localized GIST	88
C) Management of Locally advanced, metastatic, and recurrent GIST	91
D) Surgical treatment	97
1) Principles of Surgery for GIST	98
2) Resectable GIST	101
3) Surgery for Primary Resectable GISTs	102
4) Laparoscopic approach	115
5) Surgery for Metastatic, Advanced, & Drug-Resistant GISTs	116
E) Chemotherapy	118
1) Imatinib	118
2) Sunitinib	141
3) Novel Agents (Investigational Agents)	146
F) Options for liver metastasis	146
1) Surgical resection	150
2) Radiofrequency ablation (RFA)	150
3) Hepatic artery chemoembolization (HACE)	151
4) Liver transplantation.....	152
G) Survival and Follow up	153
○ Summary	155
○ References	158
○ Arabic summary	--

Dedication



To the soul of my mother



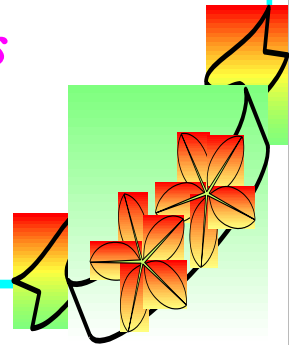
To my father



To my brother.

I dedicate this work

Wadie Boshra Gerges





*First, thanks are all due to **GOD** for Blessing this work until it has reached its end, as a part of his generous help throughout our life.*

*My profound thanks and deep appreciation to **Prof. Dr. Awad Hassan Alkayal**, Professor of General Surgery, Faculty of Medicine, Ain Shams University for his great support and advice, his valuable remarks that gave me the confidence and encouragement to fulfill this work.*

*I would like also to express my deep and special thanks to **Dr. Gamal Fawzy Samaan**, Lecturer of General Surgery, Faculty of Medicine, Ain Shams University for his generous help, guidance and patience through all the stages of this work. This work could not have reached its goal without his help.*

*I am deeply grateful to **my father and brother** who stood beside me throughout this work giving me their support.*



Wadie Boshra Gerjes

List of Figures

No.	Figure	Page
1	Interstitial cells of Cajal	10
2	Endoscopic image of GIST in fundus of stomach, seen on retroflexion	12
3	Same GIST seen on forward view of the endoscope showing overlying clot	12
4	Spindle cell GIST	16
5	Intermediate-risk GIST comprised predominantly of epithelioid cells.	16
6	Histologic spectrum of gastric GISTs.	20
7	Histologic spectrum of gastric gastrointestinal stromal tumour	21
8	Histologic spectrum of intestinal GISTs.	23
9	Histologic spectrum of small intestinal GIST	24
10	Microscopic appearance of the malignant tumor with highly cellular areas consisting of predominantly epithelioid cells	26
11	Schematic representation of KIT and platelet-derived growth factor receptor alpha (PDGFRA) molecules and KIT and PDGFRA mutations..	33
12	Schematic representation of molecular pathogenesis of GIST	33
13	Examples of KIT positivity in GISTs	41
14	Immunohistochemical spectrum of GIST	46
15	Important differential diagnoses for GIST with illustrative immunostainings	56
16	Endoscopic image of polyp in small bowel detected on double-balloon enteroscopy	65
17	A large exophytic gastric GIST arises from the greater curve. Transverse view of trans-abdominal sonography	66
18	Ultrasound showing Benign GIST of gastric body	66
19	Small gastric GIST shown by EUS.	68
20	Left parasagittal view of Transrectal sonography shows an exophytic hypoechoic mass arising from the anterolateral wall of rectum	68

List of Figures (Cont.)

No.	Figure	Page
21	Gastric GIST over the lesser curve by Barium meal	71
22	Gastrointestinal stromal tumour with central bull's eye appearance	71
23	Enteroclysis showing Distal jejunal GIST	71
24	Large ileal GIST with central necrosis, cavitation and sinus tract formation	73
25	Gastric GIST arises from greater curve with calcified foci	73
26	CT showing Jejunal GIST	74
27	Gastric GIST	74
28	Benign GIST from the lateral aspect of the gastric body.	75
29	GIST of the stomach with liver metastases.	75
30	GIST of the gastric antrum and body with extraluminal and intraluminal tumor extension	76
31	Intraluminal GIST along the lesser curve, extending into the gastrohepatic ligament	76
32	large GIST of the small bowel mesentery	77
33	GIST of the lesser curve stomach by CT, MRI, & Ultrasonography.	79
34	Rectal GIST by MRI	80
35	PET can detect imatinib response earlier than CT.	82
36	Superior mesenteric artery angiography shows GIST	83
37	GISTs with delayed images showing large draining vein, which empties into the superior mesenteric vein	84
38	Ileal GIST presented with intermittent gastrointestinal bleeding underwent Superior mesenteric angiography	84
39	Gastric GIST arises from the lesser curvature found incidentally on chest radiography	85
40	Gastric GIST arises from greater curve by chest radiography	85
41	Management of locally resectable versus advanced GISTs	88

List of Figures (Cont.)

No.	Figure	Page
42	Extraluminal growth of a small bowel gastrointestinal stromal tumour	100
43	1 Normal esophagus, 2 and 3 esophagectomy	103
44	Sagittal and transverse CT scans of a gastrointestinal stromal tumour of the gastric cardia (incidentally detected)	106
45	CT scan of a 10 × 12-cm GIST of the stomach	107
46	Gastrointestinal stromal tumour of the second part of the duodenum before and after imatinib therapy	108
47	Pre-surgery anatomy and pancreoduodenectomy either sparing the pylorus or with resection of the pylorus	109
48	CT scan of a highly malignant GIST of the proximal jejunum, closely related to but not infiltrating the mesentery of the transverse colon	111
49	CT scan of a gastrointestinal stromal tumour of the ascending colon	112
50	CT scan of a GIST of the lower rectum with presacral extension	114
51	Laparoscopic resection of 2 cm gastric GIST	116
52	Chemical structure of imatinib mesylate	120
53	Proposed recommendation for use of high-dose imatinib in metastatic patients	125
54	Hepatic artery embolization of GIST	152

List of Tables

No.	Table	Page
1	NIH Risk stratification of primary GIST according to tumour size and mitotic activity	28
2	Risk Stratification of Primary GIST by Mitotic Index, Size, and Site	30
3	RECIST and modified CT response evaluation criteria	139

List of Abbreviations

ALK	Anaplastic Lymphoma Kinase
BID	Twice daily
CB	Clinical benefit
CML	Chronic myeloid leukemia
CR	Complete response
CT	Computed Tomography
DFS	Disease free survival
DOG1	Discovered on GIST
ESMO	European Society for Medical Oncology
EUS	Endoscopic ultrasonography
GANTs	Gastrointestinal autonomic tumors
GI	Gastrointestinal
GIPACTs	Gastrointestinal pacemaker cell tumors
GISTs	Gastrointestinal stromal tumors
HACE	Hepatic arterial chemoembolization
HPF	High power field
ICCs	Interstitial cells of Cajal
LMP	Low malignant potential
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
OD	Once daily
OS	Overall survival
PAS	periodic acid Schiff
PD	Progressive disease
PDFGRA	Platelet-derived growth factor receptor alpha
PET	Positron Emission Tomography
PFS	Progression-free survival
PR	Partial response
RFA	Radiofrequency Ablation
RFS	Recurrence-free survival
SD	Stable disease
SMA	Smooth muscle actin
SUV _{max}	Maximum standardized uptake value
TKI	tyrosine kinase inhibitor
VEGFR	Vascular endothelial growth factor receptor

List of Figures

No.	Figure	Page
1	Interstitial cells of Cajal	10
2	Endoscopic image of GIST in fundus of stomach, seen on retroflexion	12
3	Same GIST seen on forward view of the endoscope showing overlying clot	12
4	Spindle cell GIST	16
5	Intermediate-risk GIST comprised predominantly of epithelioid cells.	16
6	Histologic spectrum of gastric GISTs.	20
7	Histologic spectrum of gastric gastrointestinal stromal tumour	21
8	Histologic spectrum of intestinal GISTs.	23
9	Histologic spectrum of small intestinal GIST	24
10	Microscopic appearance of the malignant tumor with highly cellular areas consisting of predominantly epithelioid cells	26
11	Schematic representation of KIT and platelet-derived growth factor receptor alpha (PDGFRA) molecules and KIT and PDGFRA mutations..	33
12	Schematic representation of molecular pathogenesis of GIST	33
13	Examples of KIT positivity in GISTs	41
14	Immunohistochemical spectrum of GIST	46
15	Important differential diagnoses for GIST with illustrative immunostainings	56
16	Endoscopic image of polyp in small bowel detected on double-balloon enteroscopy	65
17	A large exophytic gastric GIST arises from the greater curve. Transverse view of trans-abdominal sonography	66
18	Ultrasound showing Benign GIST of gastric body	66
19	Small gastric GIST shown by EUS.	68
20	Left parasagittal view of Transrectal sonography shows an exophytic hypoechoic mass arising from the anterolateral wall of rectum	68

List of Figures (Cont.)

No.	Figure	Page
21	Gastric GIST over the lesser curve by Barium meal	71
22	Gastrointestinal stromal tumour with central bull's eye appearance	71
23	Enteroclysis showing Distal jejunal GIST	71
24	Large ileal GIST with central necrosis, cavitation and sinus tract formation	73
25	Gastric GIST arises from greater curve with calcified foci	73
26	CT showing Jejunal GIST	74
27	Gastric GIST	74
28	Benign GIST from the lateral aspect of the gastric body.	75
29	GIST of the stomach with liver metastases.	75
30	GIST of the gastric antrum and body with extraluminal and intraluminal tumor extension	76
31	Intraluminal GIST along the lesser curve, extending into the gastrohepatic ligament	76
32	large GIST of the small bowel mesentery	77
33	GIST of the lesser curve stomach by CT, MRI, & Ultrasonography.	79
34	Rectal GIST by MRI	80
35	PET can detect imatinib response earlier than CT.	82
36	Superior mesenteric artery angiography shows GIST	83
37	GISTs with delayed images showing large draining vein, which empties into the superior mesenteric vein	84
38	Ileal GIST presented with intermittent gastrointestinal bleeding underwent Superior mesenteric angiography	84
39	Gastric GIST arises from the lesser curvature found incidentally on chest radiography	85
40	Gastric GIST arises from greater curve by chest radiography	85
41	Management of locally resectable versus advanced GISTs	88

List of Figures (Cont.)

No.	Figure	Page
42	Extraluminal growth of a small bowel gastrointestinal stromal tumour	100
43	1 Normal esophagus, 2 and 3 esophagectomy	103
44	Sagittal and transverse CT scans of a gastrointestinal stromal tumour of the gastric cardia (incidentally detected)	106
45	CT scan of a 10 × 12-cm GIST of the stomach	107
46	Gastrointestinal stromal tumour of the second part of the duodenum before and after imatinib therapy	108
47	Pre-surgery anatomy and pancreoduodenectomy either sparing the pylorus or with resection of the pylorus	109
48	CT scan of a highly malignant GIST of the proximal jejunum, closely related to but not infiltrating the mesentery of the transverse colon	111
49	CT scan of a gastrointestinal stromal tumour of the ascending colon	112
50	CT scan of a GIST of the lower rectum with presacral extension	114
51	Laparoscopic resection of 2 cm gastric GIST	116
52	Chemical structure of imatinib mesylate	120
53	Proposed recommendation for use of high-dose imatinib in metastatic patients	125
54	Hepatic artery embolization of GIST	152

List of Tables

No.	Table	Page
1	NIH Risk stratification of primary GIST according to tumour size and mitotic activity	28
2	Risk Stratification of Primary GIST by Mitotic Index, Size, and Site	30
3	RECIST and modified CT response evaluation criteria	139

List of Abbreviations

ALK	Anaplastic Lymphoma Kinase
BID	Twice daily
CB	Clinical benefit
CML	Chronic myeloid leukemia
CR	Complete response
CT	Computed Tomography
DFS	Disease free survival
DOG1	Discovered on GIST
ESMO	European Society for Medical Oncology
EUS	Endoscopic ultrasonography
GANTs	Gastrointestinal autonomic tumors
GI	Gastrointestinal
GIPACTs	Gastrointestinal pacemaker cell tumors
GISTs	Gastrointestinal stromal tumors
HACE	Hepatic arterial chemoembolization
HPF	High power field
ICCs	Interstitial cells of Cajal
LMP	Low malignant potential
MRI	Magnetic Resonance Imaging
NCCN	National Comprehensive Cancer Network
OD	Once daily
OS	Overall survival
PAS	periodic acid Schiff
PD	Progressive disease
PDFGRA	Platelet-derived growth factor receptor alpha
PET	Positron Emission Tomography
PFS	Progression-free survival
PR	Partial response
RFA	Radiofrequency Ablation
RFS	Recurrence-free survival
SD	Stable disease
SMA	Smooth muscle actin
SUV _{max}	Maximum standardized uptake value
TKI	tyrosine kinase inhibitor
VEGFR	Vascular endothelial growth factor receptor