Clinical cases gastric cancer

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What are Clinical Practice Guidelines?

Systematically developed evidence-based statements aiming:

1. To assist practitioners in appropriate clinical decision-making (best clinical practice)

2. To improve quality of healthcare and outcomes for patients

3. To influence national policies for efficient allocation of resources and for better delivery systems

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PROVIDE THE RIGHT CARE, AT THE RICHT TIME, FOR THE RIGHT PERSON IN THE RIGHT WAY

JAMA 2000, 284:2100-07

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History & Evolution of ESMO Guidelines

- ESMO first began to work on the development of guidelines in 1999 in order to help define the minimum standards of medical oncology practice for Eastern European countries.
- From 2001-2005 the ESMO Minimum Clinical Recommendations were published.
- In 2006 ESMO started to produce the ESMO Clinical Recommendations addressing a wider audience.
- In 2007 the Consensus Conference derived guidelines were established.
- Since 2010 they are called ESMO Clinical Practice Guidelines.

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THE STRUCTURE OF THE ESMO GLWG

Editorial Board

Chairman & Co -Chairman
2 Members
1 Ann. Oncology Executive
1 ESMO Officer

Subject Editors

1. **Breast Cancer**
2. **Gynaecological Cancer**
3. **Haematological Malignancies**
4. **Head/Neck and Lung Cancer**
5. **Urogenital Cancer**
6. **Upper and lower GI tract cancers**
7. **Pancreato-hepatobiliary cancers**
8. **Sarcomas**
9. **Supportive Care**
10. **Rare Tumours**

Reviewers

5 ESMO Faculty Members per Topic on a multidisciplinary platform

Authors

(Multidisciplinary)

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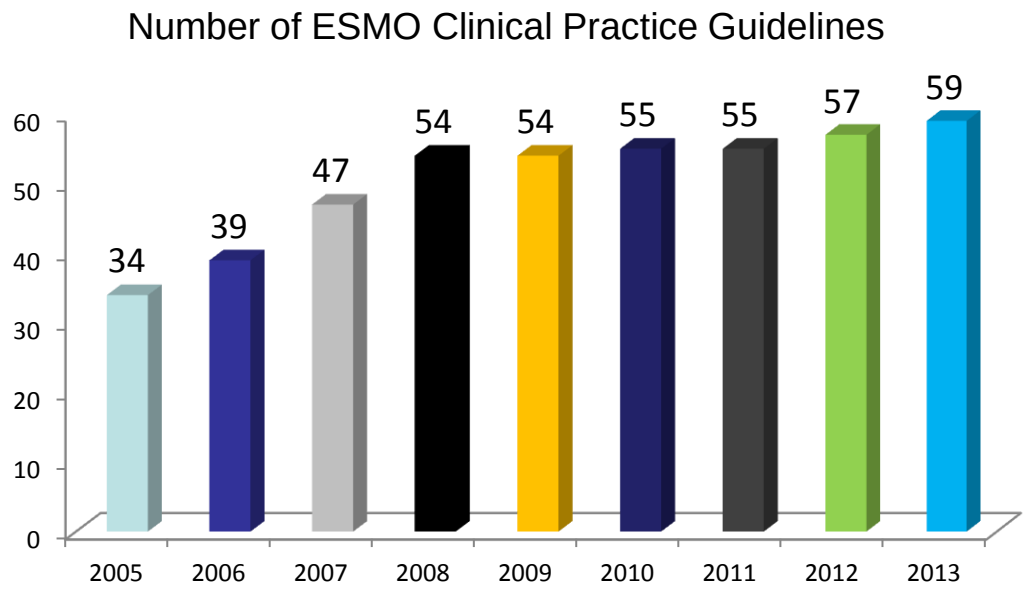
What kind of guidelines?

The Clinical Practice Guidelines

- Average number of pages: 7
- Evidence based
- Disease or topic oriented
- Available on the ESMO website
- Only those requiring update are published in Annals of Oncology



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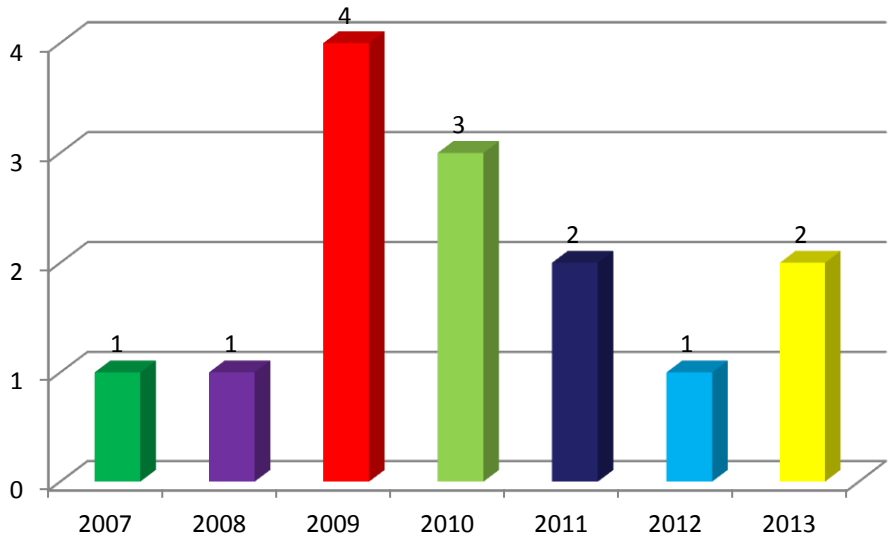
What kind of guidelines?

Consensus Conference Derived Guidelines

- To address pre-selected questions to 30-40 multidisciplinary experts on specific tumour types
- 1-2 days meeting
- Funded by ESMO or other professional networks
- Update every 2-5 years
- Published in Annals of Oncology



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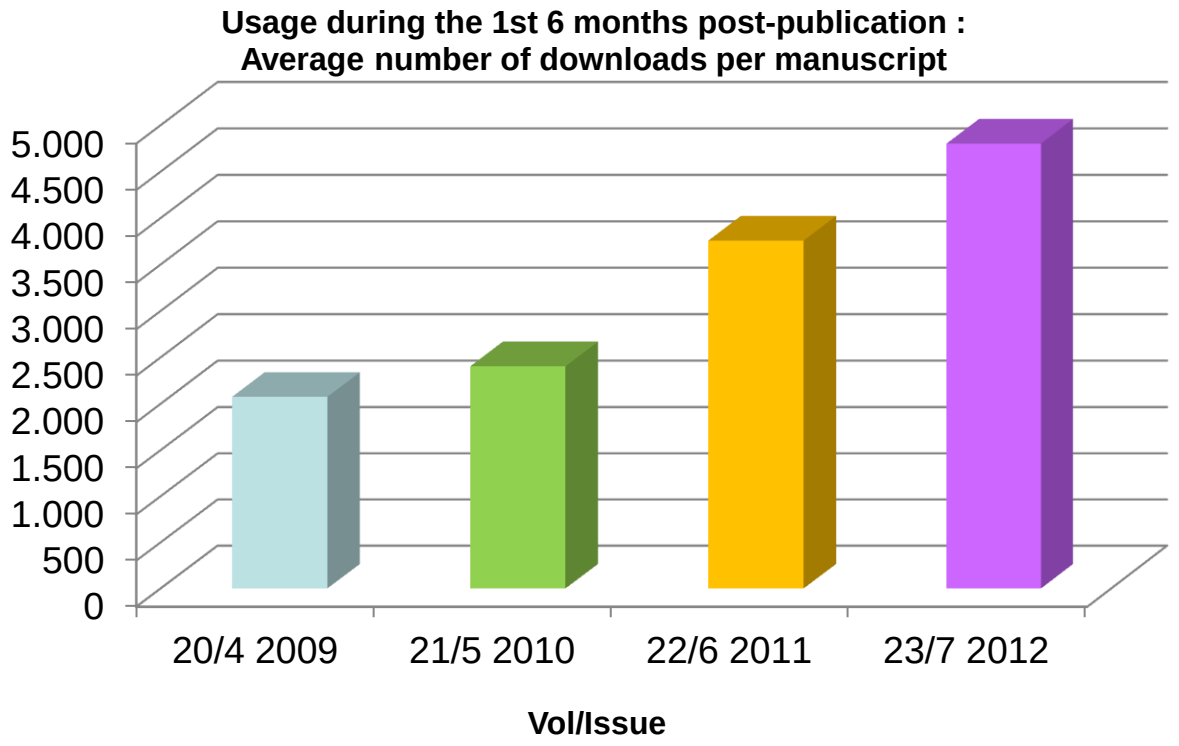
Dissemination and promotion

- Available:
  - In an annual supplement of Annals of Oncology
  - On the ESMO website (www.esmo.org)
  - On the OncologyPRO website (oncologypro.esmo.org)
- Translated:
  - Through Oxford University Press
  - In collaboration with National Cancer Societies
- Presented:
  - During Guidelines Interactive Sessions (each year since 2002).
  - To audiences of up to 3200 attendees.

ESMO CPG: overall usage figures

Downloads within first 6 months post publication:

	Total	Average per manuscript
2009 (54 manuscripts)	120309	2074
2010 (55 manuscripts)	146602	2403
2011 (13 manuscripts)	57856	3757
2012 (21 manuscripts)	105625	4801



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Supplement 2013: 20 CPG

- Gastrointestinal tumours
  - Oesophageal cancer
  - Gastric cancer
  - Primary colon cancer
  - Familial risk - colorectal cancer
  - Rectal cancer
- Breast cancer
  - Primary breast cancer
- Urogenital tumours
  - Prostate cancer
  - Testicular seminoma & non seminoma
  - Penile cancer **NEW**
- Supportive care
  - Cancer, pregnancy and fertility
- Haematological malignancies
  - Multiple myeloma
  - Acute myeloblastic leukaemia
  - Gastric marginal zone lymphoma of MALT type
  - Primary cutaneous lymphoma
  - Waldenström's macroglobulinaemia **NEW**
- Lung cancer
  - Early stage and locally advanced NSCLC
  - Small-cell lung cancer
- Gynecological tumours
  - Newly diagnosed and relapsed ovarian cancer
  - Endometrial cancer
  - Gestational trophoblastic disease **NEW**

Coming soon: Anal cancer, Bone health, High-grade malignant glioma, Myelodysplastic syndromes….

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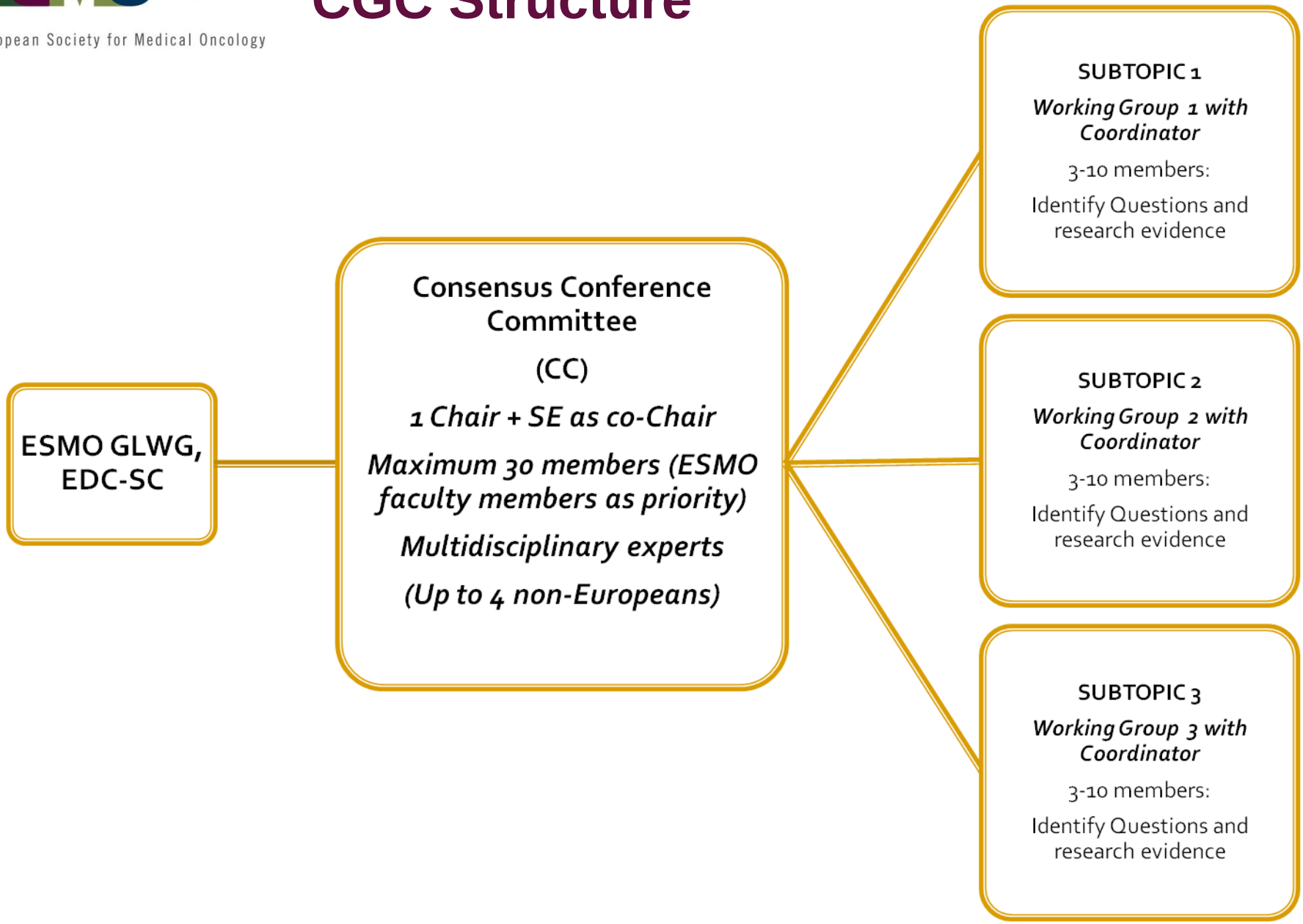
CGC Structure



Basic Methodology: Pre-conference

- Working Group (WG) responsibilities:
  - Identification of available evidence via a narrative review of the evidence. The WG Coordinators will decide how the group will work and may assign specific tasks to each WG member.
  - Study of relevant evidence (e.g. assign Questions to WG members who perform narrative review of the evidence).
  - Writing up of a report on the Questions & evidence review including a list of important references.
  - Forwarding of report to Chairs prior to the Consensus Conference.

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Basic Methodology: Conference

- The Chairs are responsible for and have authority over the conference.
- Suggested general outline (2 day conference):
  - **INTRODUCTION** with all participants.
  - **WG DISCUSSION PHASE**: Each WG to convene and discuss the subtopic.
  - **JOINT PRESENTATION PHASE**: All members meet for presentation of all WG SoERs, to be critically analyzed & discussed by all.
  - **CONCLUSION PHASE**: The CC Chairs conclude what has been discussed, agreed upon or disagreed.
  - **SUMMARY & PLANNING MEETING:** The CC Chairs and WG Chairs may spend some additional time at the end of the conference to discuss decisions and next steps.
- It is advisable to record areas of dissent.
- Following the Consensus Conference, all WGs should send their draft subtopic manuscripts (with Questions, Recommendations and Levels of Evidence) to the Chairs within 1 month.

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Basic Methodology: Post-Conference

- Chairs incorporate all draft subtopic manuscripts (with Questions, Recommendations and Levels of Evidence) in a pre-final manuscript.
- Areas of controversy and dissent are included and acknowledged in the final text. Levels of Evidence and references are provided for every formulated recommendation throughout the document. The grading system must be consistent across guidelines and the basis for the class of recommendation & levels of evidence documented.
- The pre-final manuscript is circulated to all members of the CC for a final check and comments/suggestions. The Chairs finalize the document and forward it to the GLWG and EDC-SC for approval.

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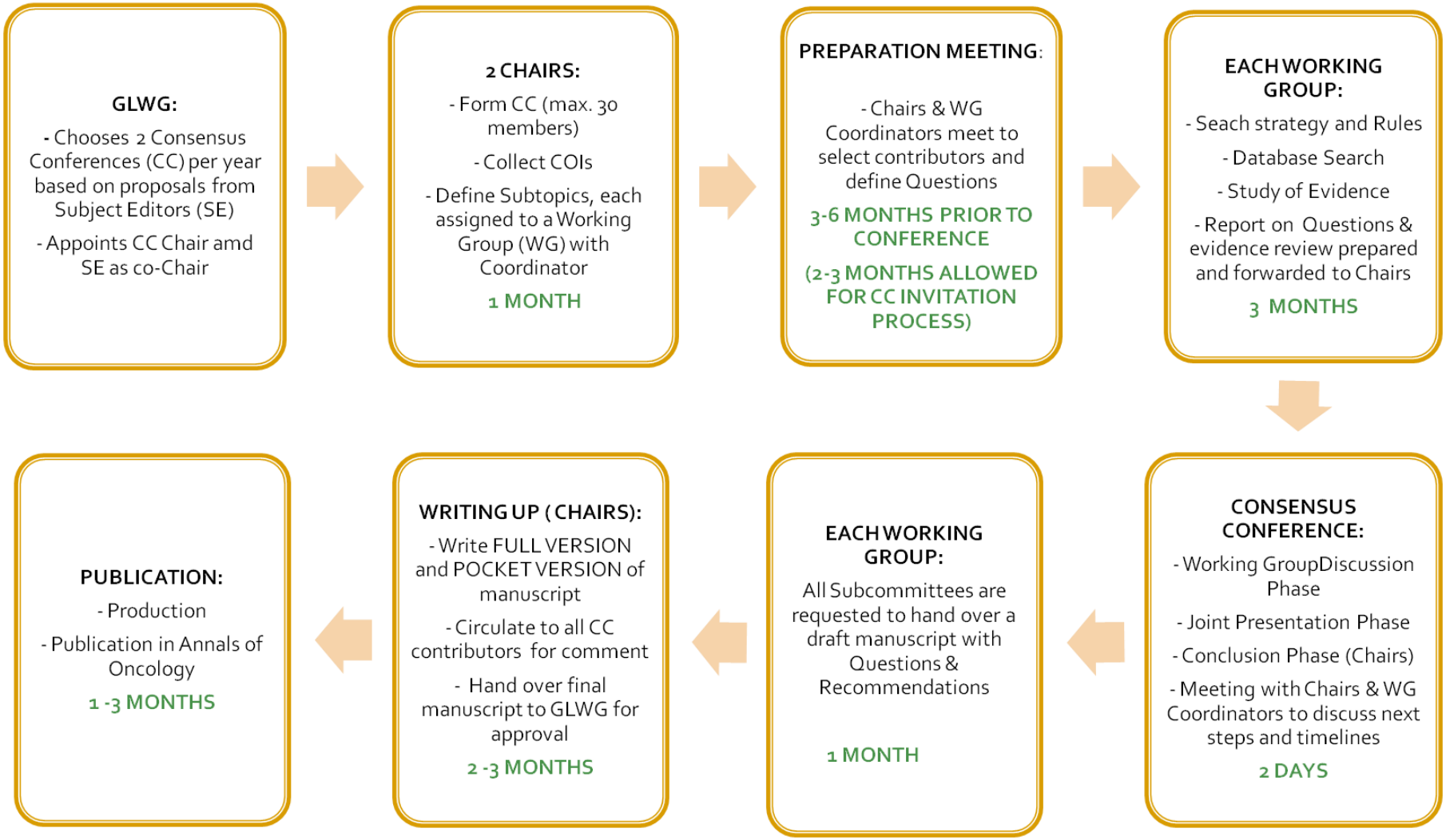
CGC Flowchart



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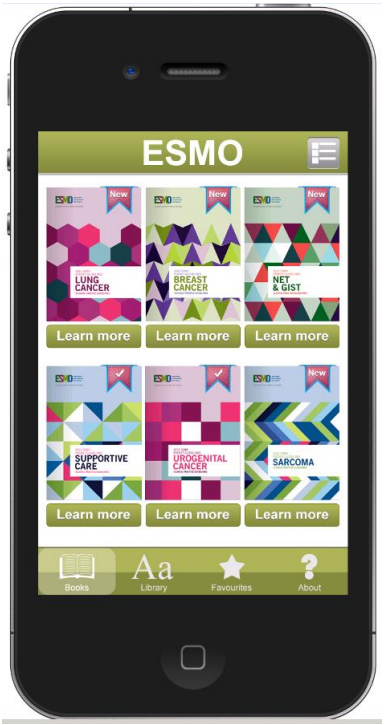
Abridged & mobile versions

- In 2012 we expanded the number of pocket guidelines and their availability by also developing a mobile library app available for Android, iTunes and iPad.
  - Six pocket guidelines published in 2012:
    - Breast Cancer
    - Lung cancer
    - Urogenital Cancer
    - NETs & GIST
    - Sarcoma
    - Supportive Care



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Pocket Guidelines

- In 2013 we have again expanded the range of pocket guidelines which now include:
  - Breast Cancer
  - Lung Cancer
  - Urogenital Cancer
  - Head & Neck Cancers (NEW)
  - Gynaecological Malignancies (NEW)
  - Upper GI Cancers (NEW)
  - Lower GI Cancers (NEW)
- 2012 titles are still valid for Sarcoma and NETs & GIST (no CPG updates)

Guides for Patients: since 2011

Guides for Patients* based on ESMO Clinical Practice Guidelines, prepared in a format your patients can easily understand

*in collaboration with Reliable Cancer Therapies

- The main goal of the project is to constantly help patients and their relatives to better understand the nature of different types of cancer and appreciate the best available treatment choices.
- Patient guides are available in different languages (English, Dutch, French, Spanish). Other languages will be added.
- Download from www.esmo.org or www.reliablecancertherapies.com
- **Online:** AML, bladder cancer, breast cancer, cervical cancer, CML, colorectal cancer, endometrial cancer, liver cancer, melanoma, non-small-cell lung cancer, oesophageal cancer, ovarian cancer, pancreatic cancer, prostate cancer, and stomach cancer
- All ESMO Guides for Patients are now included in the ESMO Cancer Guidelines mobile library

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clinical practice guidelines

Annals of Oncology 24 (Supplement 6): vi57–vi63, 2013
doi:10.1093/annonc/mdt344

Gastric cancer†: ESMO–ESSO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up

T. Waddell[1], M. Verheij[2], W. Allum[3], D. Cunningham[4], A. Cervantes[5] & D. Arnold[6]*

[1]GI Clinical Trials Unit, Royal Marsden Hospital, Sutton, UK; [2]Department of Radiation Oncology and Division of Biological Stress Response, The Netherlands Cancer Institute, Antoni van Leeuwenhoek Hospital, Amsterdam, The Netherlands; [3]Department of Surgery, Royal Marsden Hospital, London; [4]Department of Medicine, Royal Marsden Hospital, Sutton, UK; [5]Department of Hematology and Medical Oncology, INCLIVA, University of Valencia, Valencia, Spain; [6]Department of Medical Oncology, Tumor Biology Center, Freiburg, Germany

These Guidelines were developed by the European Society for Medical Oncology (ESMO), the European Society of Surgical Oncology (ESSO) and the European Society of Radiotherapy and Oncology (ESTRO) and are published jointly in the Annals of Oncology, the European Journal of Surgical Oncology and Radiotherapy & Oncology. The three societies nominated authors to write the guidelines as well as reviewers to comment on them.

These Clinical Practice Guidelines are endorsed by the Japanese Society of Medical Oncology (JSMO)

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Table 4. Levels of evidence and grades of recommendation (adapted from the Infectious Diseases Society of America-United States Public Health Service Grading System[a])

Levels of evidence	
I	Evidence from at least one large randomised, controlled trial of good methodological quality (low potential for bias) or meta-analyses of well-conducted, randomised trials without heterogeneity
II	Small randomised trials or large randomised trials with a suspicion of bias (lower methodological quality) or meta-analyses of such trials or of trials with demonstrated heterogeneity
III	Prospective cohort studies
IV	Retrospective cohort studies or case–control studies
V	Studies without control group, case reports, experts opinions
Grades of recommendation	
A	Strong evidence for efficacy with a substantial clinical benefit, strongly recommended
B	Strong or moderate evidence for efficacy but with a limited clinical benefit, generally recommended
C	Insufficient evidence for efficacy or benefit does not outweigh the risk or the disadvantages (adverse events, costs, …), optional
D	Moderate evidence against efficacy or for adverse outcome, generally not recommended
E	Strong evidence against efficacy or for adverse outcome, never recommended

[a]Dykewicz CA. Summary of the guidelines for preventing opportunistic infections among hematopoietic stem cell transplant recipients. *Clin Infect Dis* 2001; 33: 139–144. By permission of the Infectious Diseases Society of America.

Management of localized gastric cancer
Case Presentation-1

72 year old female PS 1

No relevant previous diseases

Unspecific epigastric discomfort for 2 months

Significant asthenia and weight loss for 3 months

Occasional vomiting and fullness after eating small amounts of food

A diagnostic test was done: gastroscopy

Management of localized gastric cancer
Case Presentation-1

Gastroscopy:
An ulcerated and infiltrating lesion of 5 cm was detected in the corpus/antrum of the stomach.

Multiple biopsies were done.

Poorly differentiated adenocarcinoma of the stomach of intestinal type

Staging procedures were ordered

Management of localized gastric cancer
Case Presentation-1

Chest CT-scan: no lung or mediastinal mets

Abdominal and pelvic CT-scan:

No liver mets or peritoneal mets
Thickening of the whole gastric wall without invasion of any surrounding local structures
Multiple perigastric lymph nodes of 2 cm size, but no extraperigastric and paraortic lymph nodes.

A laparoscopy and an endoscopic ultrasonography were not considered

cT3 cN+ cM0

CLASSICAL APPROACH TO LOCALISED GASTRIC CANCER

- **Surgical resection**
- **Pathology assessment and estimation of risk**
- **Treatment based upon classical TNM stage**
- **Postoperative Chemotherapy of limited value**
- **Postoperative Chemoradiation**

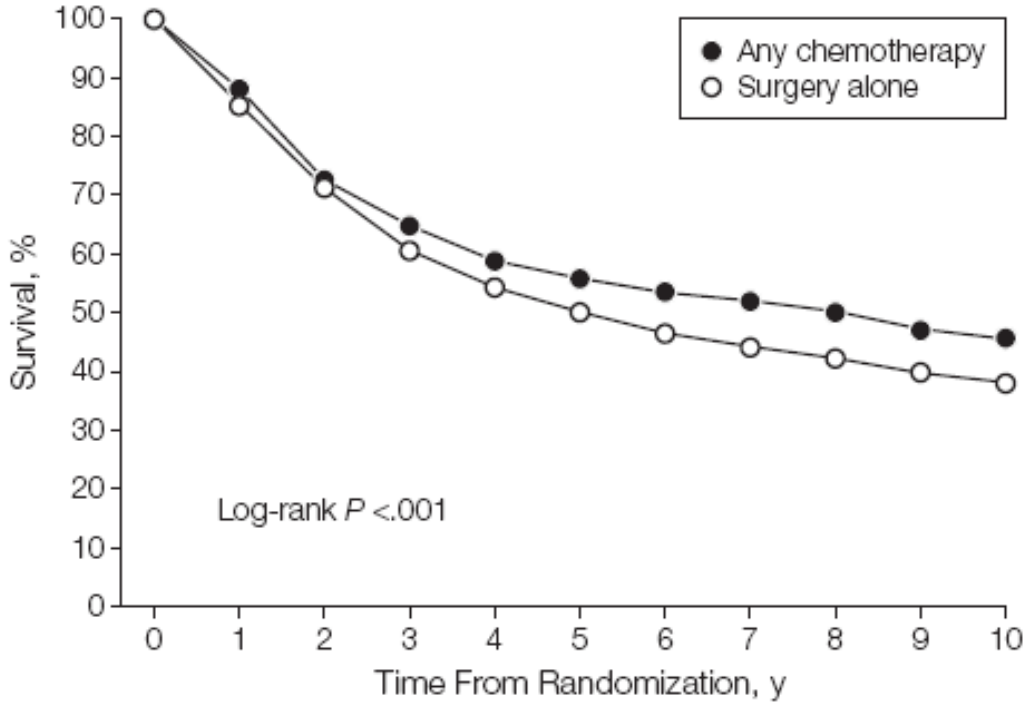
META-ANALYSIS OT TRIALS INVOLVING ADJUVANT CHEMOTHERAPY VERSUS SURGERY ALONE FOR GASTRIC CANCER-1

Meta-analysis	Year	No. Trials	No. Pts	Odds Ratio	95% CI	Conclusions
Hermanns J Clin Oncol	**1993**	**11**	**2096**	**0.88**	**0.78-1.08**	**No benefit**
Earle Eur J Cancer	**1999**	**13**	**1990**	**0.80**	**0.66-0.97**	**Small survival benefit In N+ patients**
Mari Ann Oncol	**2000**	**20**	**3658**	**0.82**	**0.75-0.89**	**Small survival benefit**
Januger Eur J Surg	**2002**	**21**	**3962**	**0.84**	**0.74-0.96**	**Very heterogeneous group of trials**
Western				0.96	0.83-1.12	
Asian				0.58	0.44-076	

META-ANALYSIS OT TRIALS INVOLVING ADJUVANT CHEMOTHERAPY VERSUS SURGERY ALONE FOR GASTRIC CANCER-2

Meta-analysis	Year	No. Trials	No. Pts	Odds Ratio	95% CI	Conclusions
Zhao et al Cancer Investigation	2008	15	3212	0.90	0.84-0.96	Marginal, though significant benefit P: 0.001
Liu et al Eur J Surg Oncol	2008	19	2286	0.85	0.80-0.90	Marginal, though significant benefit P< 0.0001
Gastric Group JAMA	2010	17	3871	0.82	0.76-090	P< 0.001

Figure 3. Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years



No. at risk

Any chemotherapy	1924	1688	1385	1217	1080	929	709	526	390	297	243
Surgery alone	1857	1568	1300	1092	952	782	583	407	267	172	138

The GASTRIC GROUP *JAMA*. 2010; 303:1729

TRIALS OF ADJUVANT CHEMOTHERAPY FOR LOCALIZED GASTRIC CANCER FROM WESTERN COUNTRIES

Trial	CT	Nr. Pts Control	Nr. Pts CT	5-year Survival Control	Median Survival CT	HR (CI at 95%)
Di Constanzo JNCI 2008	PELF	128 No CT	130	48.7%	47.6 %	0.90 0.64-1.26
Cascinu JNCI 2007	PELFw	196 FU-LV	201	50%	52%	0.95 0.70-1.29
De Vita Ann Oncol 2007	ELFE	113 No CT	113	43.5%	48%	0.91 0.69-1.21
Bajetta Ann Oncol 2002	EAP 5FU-LV	137 No CT	137	48%	52%	0.93 0.65-1.34

POSTOPERATIVE CHEMOTHERAPY IN LOCALIZED GASTRIC CANCER

- LIMITED VALUE, IF ANY
- HRs BY 0.90
- NON SIGNIFICANT EFFECT IN MOST SINGLE TRIALS
- BUT…
  - NONSTANDARDIZED SURGERY
  - MANY SINGLE TRIALS UNDERPOWERED
  - HYPOTETIC BENEFIT OVERESTIMATED
  - STRATIFIED BY MANY AND DIFFERENT CLINICAL OR PATHOLOGICAL FACTORS
  - HETEROGENEOUS POPULATION ACCRUED
  - N NEGATIVE PATIENTS PREDOMINATE
  - SELECTED POPULATION OF PATIENTS WELL ADAPTED TO TOTAL OR PARTIAL GASTRECTOMY
  - BIOLOGICAL PREDICTIVE FACTORS UNKOWN AND THEREFORE NOT APPLIED TO STRATIFICATION

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adjuvant chemotherapy

A large, individual patient-level meta-analysis of adjuvant chemotherapy in gastric cancer has confirmed a 6% absolute benefit for 5-FU-based chemotherapy compared with surgery alone (HR 0.82, 95% CI 0.76–0.90; $P < 0.001$) in all subgroups tested [25] [I, A].

Gastric cancer†: ESMO–ESSO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up

T. Waddell[1], M. Verheij[2], W. Allum[3], D. Cunningham[4], A. Cervantes[5] & D. Arnold[6*]

CURRENT APPROACH TO LOCALISED GASTRIC CANCER

- Clinical staging with CT-Scan/endoscopic ultrasonography
- Preoperative Chemotherapy if cT3-4 or cN+
- Surgical resection
- Pathology assessment and estimation of risk
- Postoperative Chemotherapy if feasible

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day D1-5) [18]. Perioperative chemotherapy has therefore been widely adopted as the standard of care throughout most of the UK and Europe [I, A]. Since capecitabine avoids the need for an indwelling central venous access device, and is non-inferior to 5-FU in the advanced disease setting [19], many centres use ECX (epirubicin, cisplatin, capecitabine) perioperatively in preference to ECF [IV, C]. Other platinum / fluoropyrimidine doublets may be considered in patients with specific drug contraindications.

Gastric cancer†: ESMO–ESSO–ESTRO Clinical Practice Guidelines for diagnosis, treatment and follow-up

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Management of localized gastric cancer
Case Presentation-1

Three courses of preoperative chemotherapy with Cape/Ox were given with good tolerance

D2 surgical resection and partial gastrectomy was performed:

No peritoneal or liver mets were seen

The pathology report indicated:
Intestinal type poorly differentiated adenocarcinoma invading muscular layer but not beyond
One tumor-involved out of 26 lymph nodes found in the perigastric fat. No lymph nodes involved out of 19 in the extraperigastric areas

ypT2 ypN1/36 M0

Management of localized gastric cancer
Case Presentation-1

Three courses of **preoperative chemotherapy** with Cape/Ox were planned after surgical resection

Due to surgical related morbidities no postoperative chemotherapy could be given

The patient is doing well with no symptoms or signs of relapsing disease 48 months after surgery

Management of localized gastro-esophageal junction cancer
Case Presentation-2

56 year old female PS 1

No relevant previous diseases

Overweight (BMI: 29) and active smoker

Dysfagia for 2 months

Isolated episodes of gastrointestinal bleeding with dark stools

Weight loss less than 5%

A diagnostic test was done: gastroscopy

Management of localized gastro-esophageal junction cancer
Case Presentation-2

Gastroscopy:
An ulcerated and infiltrating hemicircumferential lesion of 5 cm was detected starting at 32 cm of the mouthand reaching the gastroesophageal junctio. No other alterations in the stomach.

Multiple biopsies were done.

Moderately differentiated adenocarcinoma of the stomach of diffuse type

Staging procedures were ordered

Management of localized gastro-esophageal junction cancer: Case Presentation-2

Chest Abdominal and pelvic CT-scan:

No lung or mediastinal mets

No liver mets or peritoneal mets

Bulhy tumor involving the lower third of the esophagus and reaching the GE junction.

Complete thickening of the whole esophageal wall without invasion of any surrounding local structures

Multiple lymph nodes of 2 cm size at the celiac and paraortic areas.

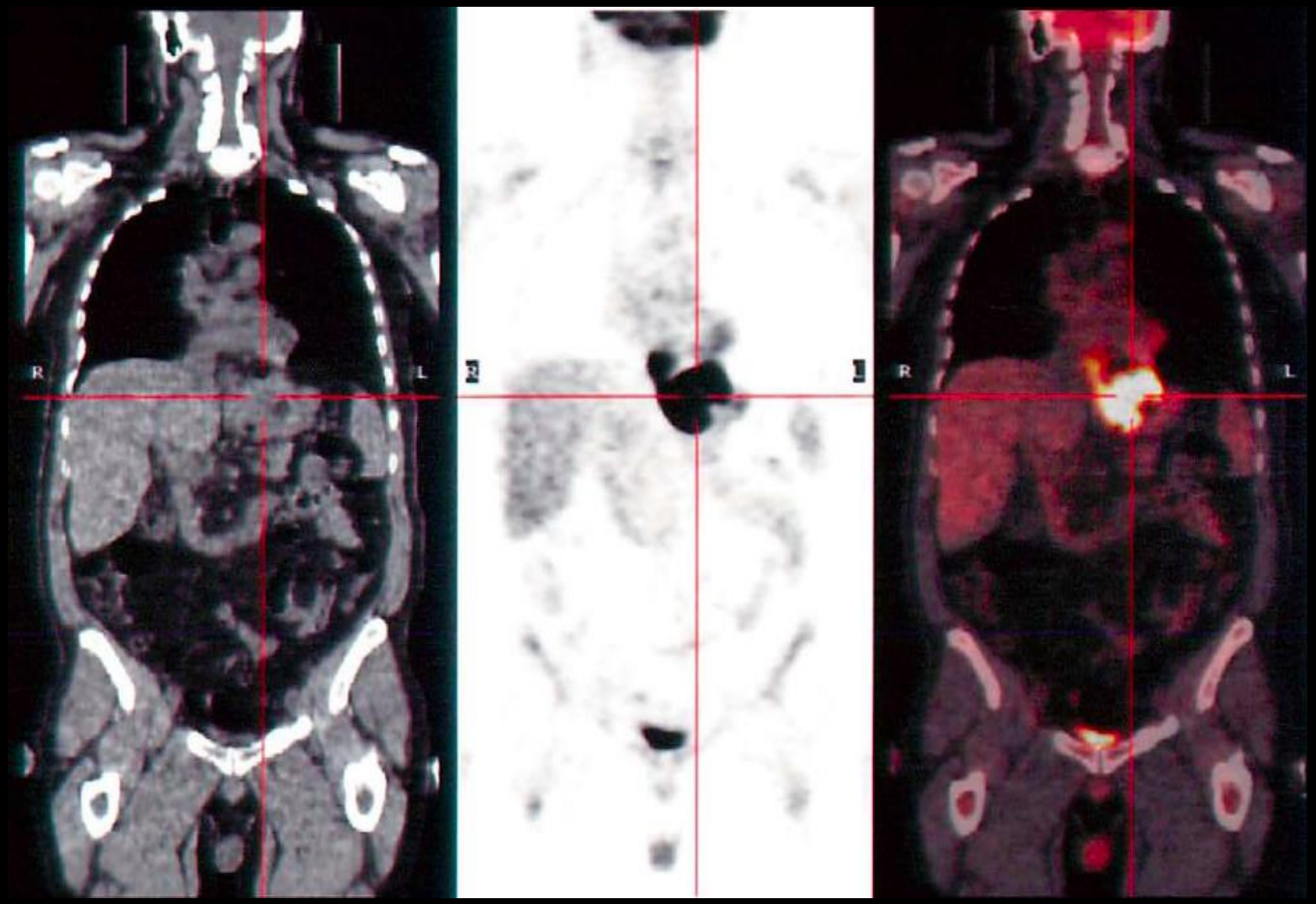
cT3 cN+/- cM0

Management of localized gastro-esophageal junction cancer: Case Presentation-2

A laparoscopy and an endoscopic ultrasonography were not considered

PET CT did not show metastatic spots. An hypermetabolic area (SUV: 16,2) within the GE junction was found. No nodal metabolic activity was detected

cT3 cN+/- cM0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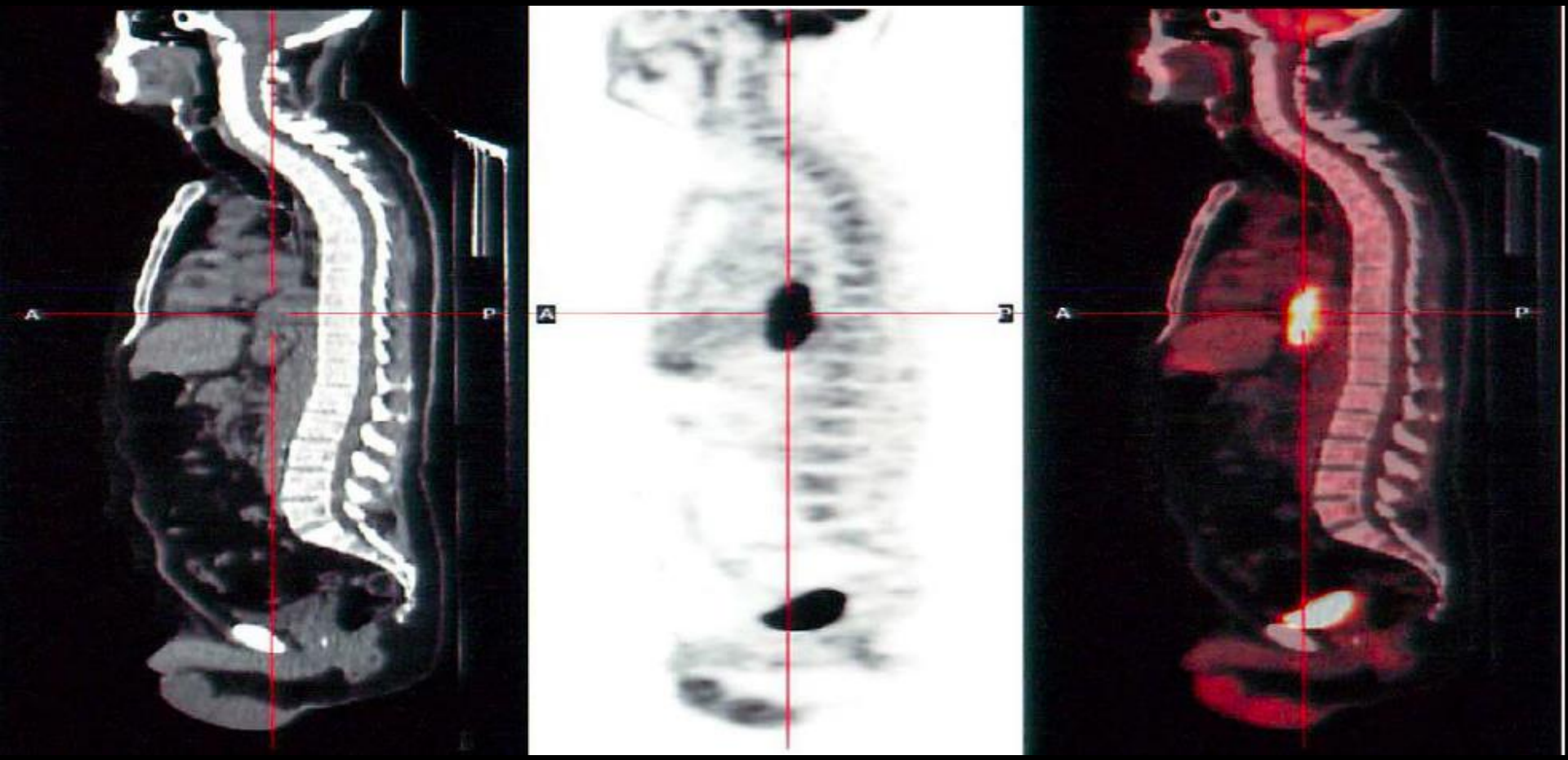
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Management of localized gastro-esophageal junction cancer: Case Presentation-2

Three courses of **preoperative chemotherapy** with Cape/Ox were given with good tolerance
Dysphagia disappeared after starting CT

An extended Esophagectomy plus partial gastrectomy with a thoracoabdominal approach was performed. Mediastinal and D2 lymphadenectomy.
No peritoneal or liver mets were seen

Management of localized gastro-esophageal junction cancer: Case Presentation-2

The pathology report indicated:

Diffuse type moderately differentiated adenocarcinoma invading submucosa at the esophagus but invading subserosal fat at the cardia level.

No medistinal nodes involved out of 11resected.
No lymph nodes involved out of 16 analysed in the perigastric and extraperigastric areas

ypT3 ypN0 M0

Management of localized gastro-esophageal junction cancer: Case Presentation-2

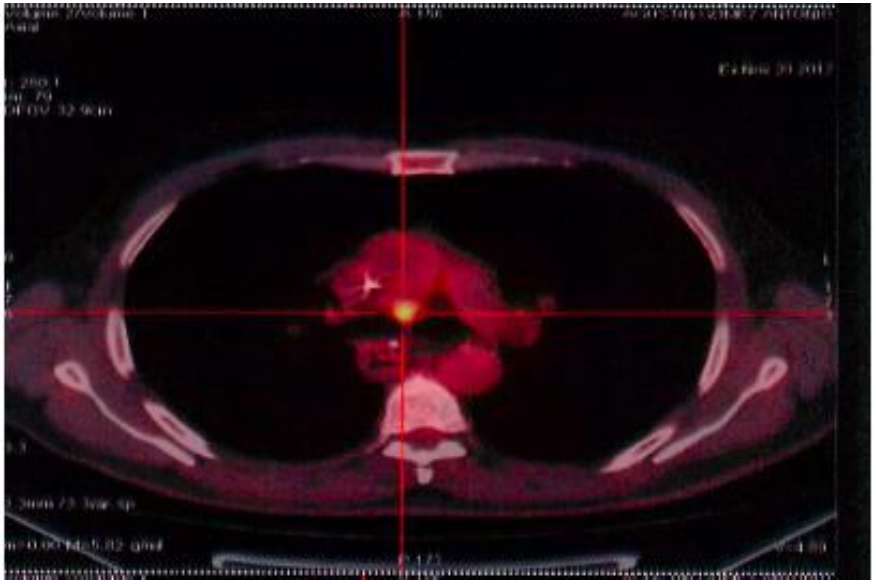
Three courses of preoperative chemotherapy with Cape/Ox were given after surgical resection starting 6 weeks thereafter

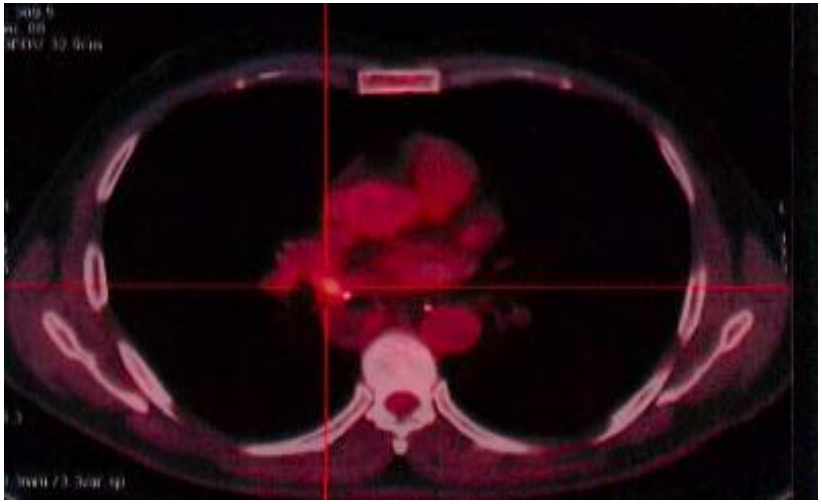
The patient was doing well with no symptoms or signs of relapsing disease 30 months after surgery

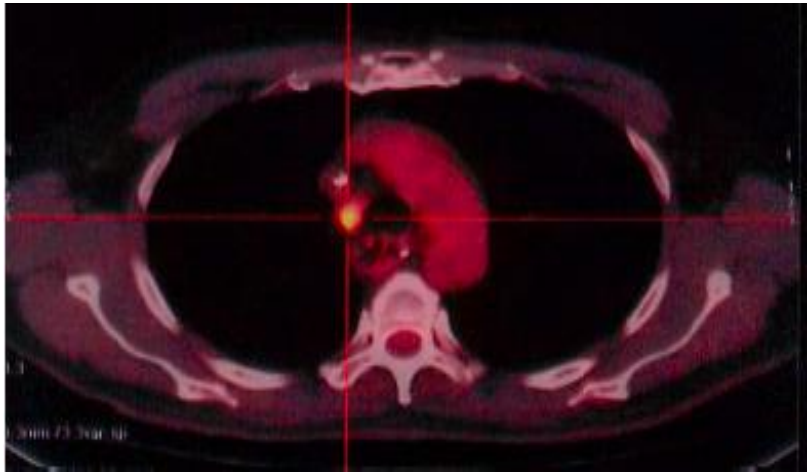
A CT scan was done every year and showed three mediastinal lymph nodes increasing in size (12 mm) at areas 4, 7 and precarinal.

An Endobronchial US with biopsy confirmed a mediastinal relapse in all three nodes detected

A PET-CT did not find any other mets







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