Timing of Adjuvant Chemotherapy & Its Association with Survival in Patients with Colorectal Cancer, A Retrospective Analysis

Thesis

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By

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List of Abbreviations

Abb.	Full term
AC	*Adjuvant chemotherapy*
APC	*Adenomatous polyposis coli*
ASCO	*American society of clinical oncology*
BMI	*Body mass index*
Capeox	*Capecitbine, oxaliplatin*
CEA	*Carcinoembryonic antigen*
CIMP	*CpG island methylator phenotype*
CK	*Cytokeratin*
CRC	*Colorectal cancer*
CRCSC	*Colorectal cancer subtyping consortium*
CRM	*Circumferential resection margin*
CT DNA	*Cell free tumor DNA*
CTCs	*Circulating tumor cells*
DFS	*Disease-free survival*
DM	*Diabetes mellitus*
EGFR	*Epidermal growth factor receptor*
EpCAM	*Epithelial adhesion molecule*
FAP	*Familial adenomatous polyposis*
FIT	*Fecal immunhistochemical test*
Folfox	*Oxaliplatin, leucovorin, 5-fluorouracil*
gFOBT	*Guiac-based fecal occult blood test*
HNPCC	*Hereditary non polyposis colorectal cancer*
IBD	*Inflammatory bowel disease*
IGF-I	*Insulin like growth factor 1*
IO	*Intestinal obstruction*
K-RAS	*Kristen rat sarcoma*
LN	*Lymph node*
LVI	*Lymphovascular invasion*

List of Abbreviations cont...

Abb.	Full term
MAP	*MutY human homolog MUTYH associated polyposis*
MMR	*Mismatch repair*
MSI	*Microsatellite instability*
NCCN	*National comprehensive cancer network*
OS	*Overall survival*
PCR	*Polymerase chain reaction*
PNI	*Perineural invasion*
SSPs	*Sessile serrated polyps*
TNM	*Tumor, node, metastasis*
WC	*Waist circumference*

INTRODUCTION

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States ***(Siegel et al., 2018)***.

Although surgical resection is the main core of management for patients with stage I-III disease, a significant amount of patients may eventually relapse and die from their disease. Large randomized clinical trials of adjuvant chemotherapy after curative resection of CRC have shown improvement in survival, which determines the current standard of care ***("NIH consensus conference. Adjuvant therapy for patients with colon and rectal cancer," 1990).*** Adjuvant chemotherapy (AC) is generally recommended after curative surgical resection of stage III colon cancer and stage II colon cancer in which high risk features are present including T4 tumors, poorly differentiated histology (exclusive of cancers that are MSI-H), lymphovascular inavasion, perineural invasion, bowel obstruction, lesions with localized perforation or close, indeterminate or positive margins or inadequately sampled nodes (less than 12 lymph nodes) ***(Des Guetz et al., 2010; Benson et al., 2004).***

However, the optimal time from surgery to the start of chemotherapy in CRC is not known.

Because most clinical trials recommend starting AC within 6 to 8 weeks after surgery, a routine clinical assumption is that chemotherapy should commence as soon as practical. Also, it is presumed that chemotherapy has little or no benefit beyond a 3 month delay. There is no direct evidence to support any of these assumptions. Reasons for a delay in time to AC maybe attributed to patient factors such as postoperative complications or comorbid conditions or health-system logistic factors such as delays in referral or wait times. The question of time to AC is an important one. Timely access to AC is often considered as a quality indicator ***(Figueredo et al., 2004).***

Furthermore, beyond a certain time frame from surgery, such as the often quoted 12 weeks, it is uncertain whether the adjuvant benefit diminishes or is even totally lost.

A systematic review & meta-analysis of 10 studies involving more than 15,000 patients tested the effect of timing of adjuvant therapy after resection. Results of this analysis have demonstrated that each 4 week delay in chemotherapy results in a 14% decrease in OS, indicating that adjuvant chemotherapy should be administrated as soon as the patient is medically able ***(Biagi et al., 2011).***

AIM OF THE WORK

The objectives of this study are:

- To determine the impact of delay of adjuvant chemotherapy on survival in colorectal cancer in terms of Overall survival (OS) and Disease free survival (DFS).
- To identify the causes of delay of start of adjuvant chemotherapy.

Review of Literature

Epidemiology

Colorectal cancer is the third most common cancer among men & women accounting for 10.2% of new cases in men & 9.5% in women in 2018 & the fourth leading cause of cancer death in males & third leading cause of cancer death in females worldwide. Over 1.8 million new colorectal cancer cases and 881,000 deaths are estimated to occur in 2018, accounting for about 1 in 10 cancer cases and deaths. Colorectal cancer is placed third in terms of incidence and second in terms of mortality ***(Bray et al., 2018).***

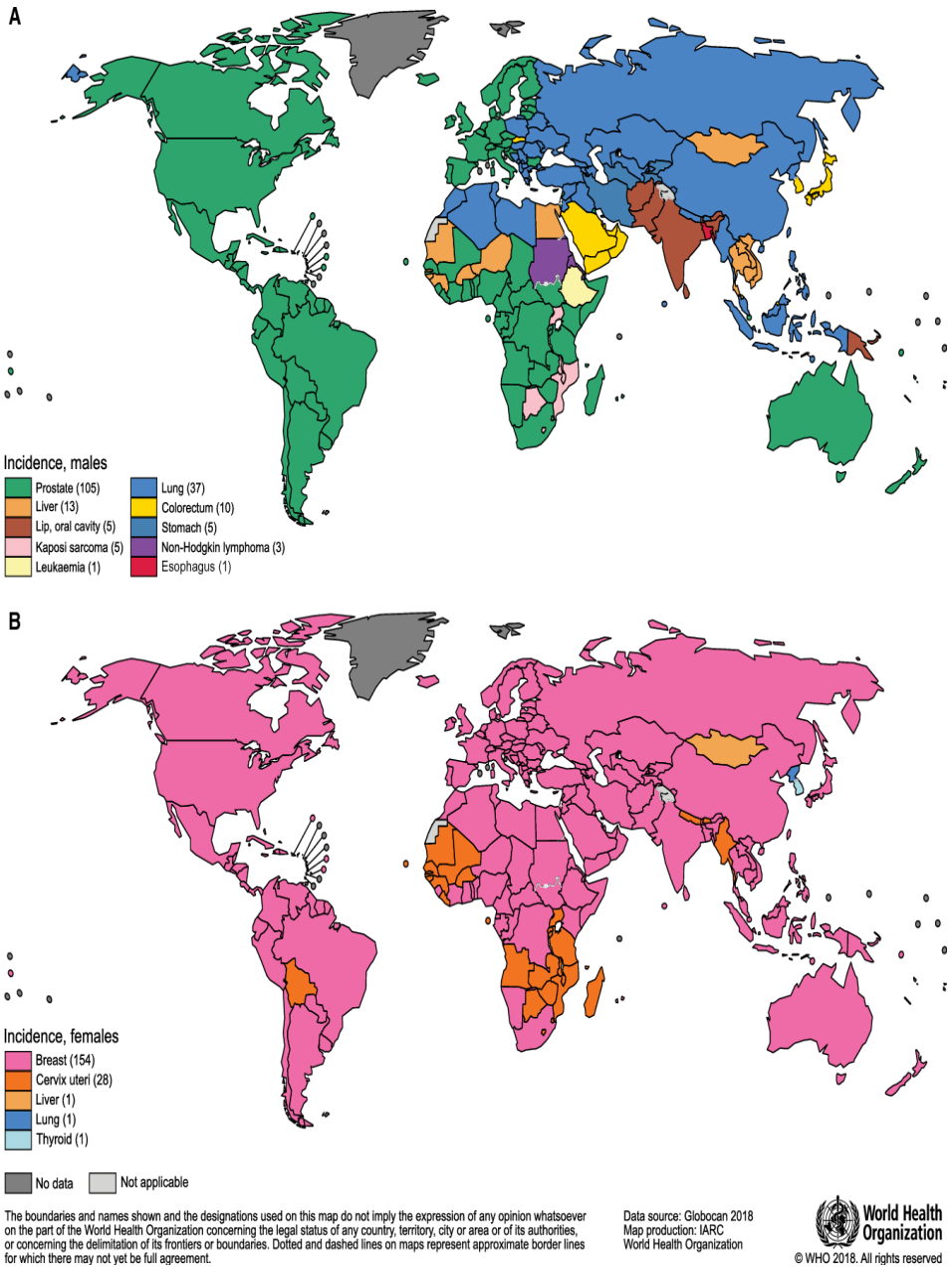

Figure 1: Global Maps Presenting the Most Common Type of Cancer Incidence in 2018 in Each Country Among (A) Men and (B) Women.

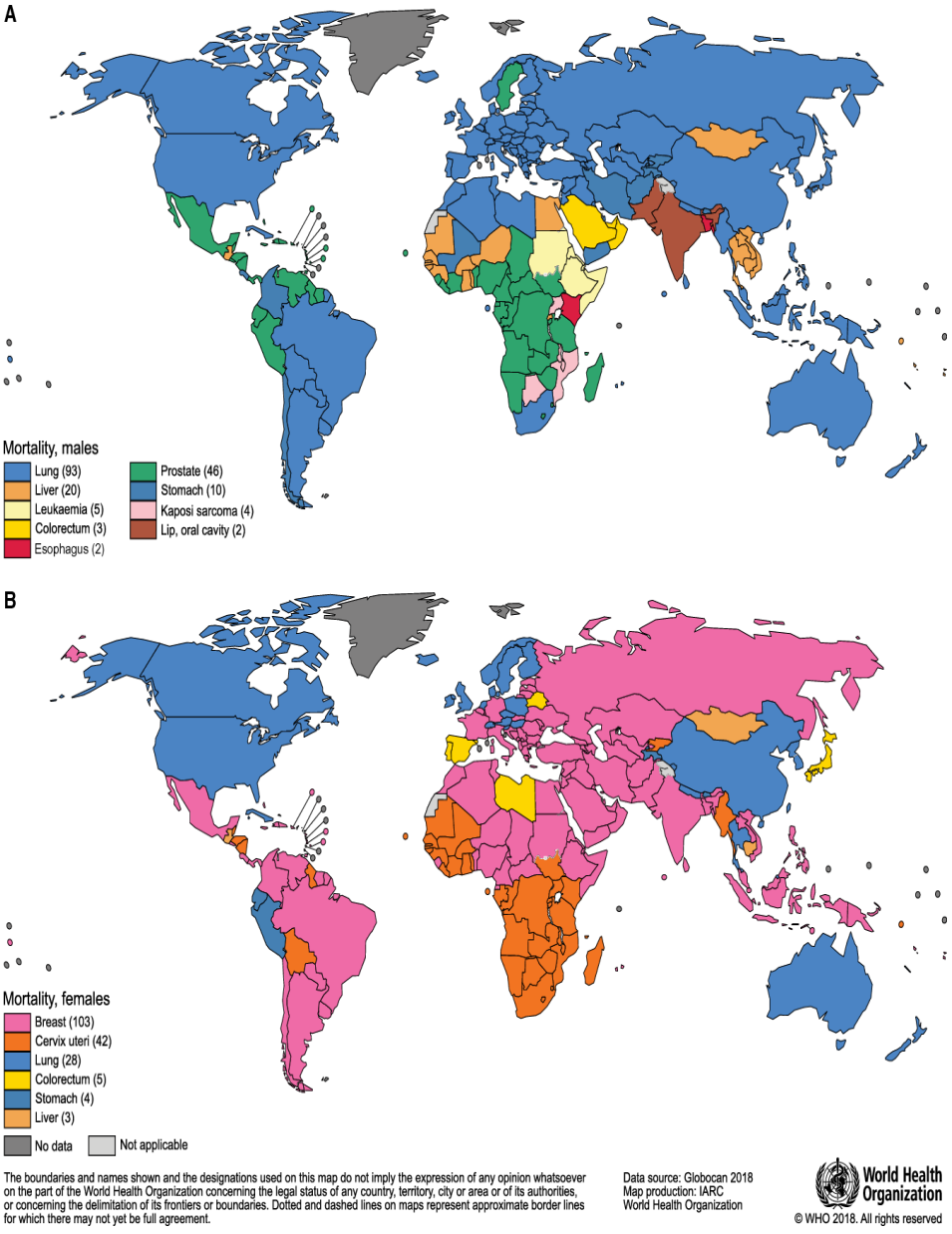

Figure 2: Global Maps Presenting the Most Common Type of Cancer Mortality by Country in 2018 Among (A) Men and (B) Women.