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Chinese Session

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The Role of Forkhead Box Transcription Factors in Hepatocellular Carcinoma Metastasis

Limin Xia

Xijing Hospital of Digestive Disease
Fourth military medical university
Xi’an, China
Metastasis is the major reason for the high mortality of HCC patients
Screening of genes from human HCC tissues

Metastatic HCC tissues VS Primary HCC tissues

Metastatic HCC

Downregulated:
- FoxA1
- FoxA2
- FoxD3
- FoxO1
- FoxO3A

Upregulated:
- FoxJ1
- FoxQ1
- FoxK1
- FoxM1
- FoxC1
Forkhead box transcription factor family

Three dimensional structure

- 41 genes identified in humans
- A wide spectrum of biological processes, including metabolism, development, differentiation, proliferation, and apoptosis

Nat Rev Immunol. 2018
Nat Rev Cancer. 2013
The role of Fox in cancer progression

FoxA
Endocrine-independent proliferation and survival

FoxM
Uncontrolled cell proliferation

FoxO
Resistance to apoptosis

FoxP
Evasion of tumor immune surveillance

Tumorigenesis and cancer progression

Front Immunol. 2017
Trends Genet. 2011
Nat Rev Cancer. 2007
Fox genes are closely related to inflammation and metastasis.
Our study on Fox genes in HCC metastasis

- IL-8
- TNF-α
- FoxC1
- FoxQ1
- FoxM1
- Snai1
- CCL2
- ZEB2
- Twist1
- MMP7
- CCL2

Invasion and metastasis

Recruit and educate

IL-8
IL-6
TNF-α

Change microenvironment

References:
- J Hepatol. 2012 Sep;57(3):600-12.
- Oncogene. 2018 Jun 8 [Epub ahead of print]
The biological function of FoxC1

TAD: transactivation domain

Wnt

EGF/ERK

FoxC1

VEGF

Notch1

DLL4

blood vessel maturation

Nat Genet. 2009
Nat Rev Genet. 2009
Part I  FoxC1 promotes HCC metastasis
FoxC1 is significantly upregulated in HCC tissues

<table>
<thead>
<tr>
<th>FoxC1 staining</th>
<th>Tumor (n=406)</th>
<th>Adjacent nontumor (n=406)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive</td>
<td>257</td>
<td>98</td>
<td>P&lt;0.001</td>
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<tr>
<td>Negative</td>
<td>149</td>
<td>308</td>
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</table>
FoxC1 overexpression predicts poor prognosis
## Correlation Between FoxC1 Expression and Clinicopathological Characteristics in 406 HCCs

<table>
<thead>
<tr>
<th>Clinicopathological variables</th>
<th>Tumor FoxC1 expression</th>
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<tr>
<td></td>
<td>Negative (n=149)</td>
<td>Positive (n=257)</td>
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<tr>
<td>Maximal tumor size</td>
<td>98</td>
<td>136</td>
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<tr>
<td></td>
<td>51</td>
<td>121</td>
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<tr>
<td>Tumor encapsulation</td>
<td>34</td>
<td>83</td>
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<tr>
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<td>115</td>
<td>174</td>
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<tr>
<td>Microvascular invasion</td>
<td>98</td>
<td>131</td>
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<td></td>
<td>51</td>
<td>126</td>
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<tr>
<td>Tumor differentiation</td>
<td>124</td>
<td>181</td>
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<td>25</td>
<td>76</td>
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<td>TNM stage</td>
<td>128</td>
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## Multivariate analysis of factors associated with recurrence of 406 HCCs

<table>
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<th>Variables</th>
<th>multivariate analysis</th>
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<tbody>
<tr>
<td></td>
<td>Recurrence</td>
<td>HR</td>
<td>95% CI</td>
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<tr>
<td>Maximal tumor size (≤5 versus &gt;5 cm)</td>
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<td>0.965</td>
<td>0.724-1.288</td>
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<tr>
<td>Tumor encapsulation (absent versus present)</td>
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<td>1.276</td>
<td>0.902-1.805</td>
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<tr>
<td>Microvascular invasion (absent versus present)</td>
<td></td>
<td>0.75</td>
<td>0.538-1.046</td>
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<tr>
<td>Tumor differentiation (I-II versus III-IV)</td>
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<td>0.455</td>
<td>0.310-0.699</td>
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<tr>
<td>TNM stage (I-II versus III)</td>
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<td>0.44</td>
<td>0.310-0.669</td>
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<tr>
<td>FoxC1 expression (negative versus positive)</td>
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<td>0.649</td>
<td>0.495-0.852</td>
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</table>
### Multivariate analysis of factors associated with survival of 406 HCCs

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<tr>
<th>Variables</th>
<th>Survival</th>
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<td>Maximal tumor size ((\leq 5) versus &gt;5 cm)</td>
<td>HR</td>
<td>95% CI</td>
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<tr>
<td>Tumor encapsulation (absent versus present)</td>
<td>0.934</td>
<td>0.703-1.241</td>
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<td>Microvascular invasion (absent versus present)</td>
<td>1.225</td>
<td>0.877-1.712</td>
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<tr>
<td>Tumor differentiation (I-II versus III-IV)</td>
<td>0.745</td>
<td>0.534-1.039</td>
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<td>TNM stage (I-II versus III)</td>
<td>0.43</td>
<td>0.295-0.628</td>
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<tr>
<td>FoxC1 expression (negative versus positive)</td>
<td>0.475</td>
<td>0.293-0.771</td>
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<tr>
<td>FoxC1 expression (negative versus positive)</td>
<td>0.641</td>
<td>0.491-0.837</td>
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FoxC1 promotes HCC invasion and metastasis

A

Migration

Invasion

B

Primary tumor

Lung metastasis

C

Incidence of lung metastasis in transplanted nude mice

<table>
<thead>
<tr>
<th></th>
<th>Lung metastasis</th>
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<tbody>
<tr>
<td>SMMC7721-control</td>
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<tr>
<td>SMMC7721-FoxC1</td>
<td>6/10</td>
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<tr>
<td>HCCLM3-shcontrol</td>
<td>10/10</td>
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<tr>
<td>HCCLM3-shFoxC1</td>
<td>5/10</td>
</tr>
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</table>
Identification of FoxC1 target genes using ChIP-sequencing and RNA-sequencing

Huh7-control → ChIP-seq → RNA-seq → Target genes

Snai1, BOC, MMP9, AOC3, VCAN, CCKAR, NEDD9, MAP4K1, CD24, CNTN2, CXCR1, CCL2, CTNNB1, COL1A2, VIM, ITGA5, FN1

EMT regulator

Snai1

Metastasis regulator

NEDD9

Inflammatory mediator

CCL2, CXCR1
FoxC1 induces EMT in HCC cells
Loss of E-cadherin is a hallmark of EMT

FoxC1

Snai1  Twist  Slug  ZEB1  SIP1

E-box  E-box  E-box  E-cadherin promoter

Loss of E-cadherin

Snai1 is critical for FoxC1-induced loss of E-cadherin expression
Snai1 is critical for FoxC1-induced HCC invasion and metastasis

**A**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Migrated per field</th>
<th>Invaded per field</th>
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<tr>
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<tr>
<td>SMMC7721-FoxC1</td>
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</tr>
<tr>
<td>SMMC7721-FoxC1+LV-shcontrol</td>
<td><img src="image" alt="Graph" /></td>
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<tr>
<td>SMMC7721-FoxC1+LV-shSnai1</td>
<td><img src="image" alt="Graph" /></td>
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</table>

**B**

- SMMC7721-FoxC1 + LV-shcontrol
- SMMC7721-FoxC1 + LV-shSnai1

Primary tumor

**C**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Incidence of lung metastasis in transplanted nude mice</th>
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</thead>
<tbody>
<tr>
<td>SMMC7721-FoxC1 + LV-shcontrol</td>
<td>5/10</td>
</tr>
<tr>
<td>SMMC7721-FoxC1 + LV-shSnai1</td>
<td>1/10</td>
</tr>
</tbody>
</table>

Lung metastasis
NEDD9 promotes cancer metastasis

- Wnt
- TGF-β
- Hypoxia
- NEDD9
- FAK
- Cytoskeleton remodeling
- Distant metastasis
- Melanoma
- Breast cancer
- Colon cancer

Integrins

Cancer Cell. 2008
NEDD9 is a direct transcriptional target of FoxC1
Knockdown of NEDD9 significantly attenuated FoxC1-enhanced invasion and metastasis.
Summary

- FoxC1
- Snai1
- NEDD9
- E-cadherin
- E-cadherin loss
- NEDD9
- EMT
- Migration
- Metastasis

Part II  FoxC1 plays a critical role in inflammation-mediated HCC metastasis
Pro-inflammatory cytokines produced in the tumor microenvironment facilitate tumor metastasis

Hepatocytes

Oxidative stress DNA damage

Apoptotic hepatocytes

IL-6, IL-8, IGFBP7

Oxidative stress oncogene activation (nRas, myc)

Senescent hepatocytes

Immune surveillance

MΦ

Immune escape

CD4+ T

Clearance

Transformed hepatocytes

(2nd Hit)

Hepatocellular carcinoma

Trends Immunol. 2018
Hepatology. 2012
IL-8 is an important pro-inflammatory mediator in tumor microenvironment

- **tumor cell**
  - CXCR1
  - Rho/ROCK
  - Cancer cell motility

- **Macrophage**
  - CXCR2
  - Endothelial cell
  - Angiogenesis

- **CXCR1/2**
  - Leukocyte
  - Proinflammatory cytokines secretion

- **Recruit**

- **Metastasis**

Theranostics. 2017
Nat Rev Immunol. 2011
IL-8 up-regulates FoxC1 expression in HCC cells
Knockdown of FoxC1 decreases IL-8-enhanced HCC metastasis

<table>
<thead>
<tr>
<th>Incidence of lung metastasis in transplanted nude mice</th>
<th>Lung metastasis</th>
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<tbody>
<tr>
<td>Huh7-control</td>
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<tr>
<td>Huh7-IL-8</td>
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<td>Huh7-IL-8+LV-shcontrol</td>
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<td>Huh7-IL-8+LV-shFoxC1</td>
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Up-regulation of FoxC1 rescues the decreased HCC metastasis induced by IL-8 knockdown
List of genes differentially expressed in Huh7 cells after FoxC1 over-expression using a human Chemokines and Receptors PCR array

<table>
<thead>
<tr>
<th>Gene</th>
<th>Huh7-FoxC1 (fold change)</th>
<th>Function</th>
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<tbody>
<tr>
<td>CCL2</td>
<td>4.56</td>
<td>Chemokine (C-C motif) Ligands</td>
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<tr>
<td>CXCL5</td>
<td>4.41</td>
<td>Chemokine (C-X-C motif) Ligands</td>
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<tr>
<td>MMP7</td>
<td>3.38</td>
<td>Other Chemokines and Related Genes</td>
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<tr>
<td>IL8RA(CXCR1)</td>
<td>3.36</td>
<td>Other Chemokines and Related Genes</td>
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<tr>
<td>SDF2</td>
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<td>Other Chemokines and Related Genes</td>
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<td>CCRL2</td>
<td>2.52</td>
<td>Chemokine (C-C motif) Receptors</td>
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<td>TNFRSF1A</td>
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<td>GPR31</td>
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<td>CXCR4</td>
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<td>Chemokine (C-X-C motif) Receptors</td>
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<td>Chemokine (C-C motif) Ligands</td>
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<td>MYD88</td>
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<tr>
<td>CCR2</td>
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<td>Chemokine (C-C motif) Receptors</td>
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<tr>
<td>CKLFSF3</td>
<td>2.06</td>
<td>Other Chemokines and Related Genes</td>
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</tbody>
</table>
FoxC1 promotes CCL2 secretion in human HCC cells

- SMMC 7721
- Huh7

- MHCC 97H
- HCCLM3

**Gene Expression**

- LV-control
- LV-FoxC1
- LV-shFoxC1

**CCL2 Secretion**

- LV-control
- LV-FoxC1
- LV-shFoxC1

*Significant differences indicated by asterisks and arrows.*
FoxC1 up-regulates CXCR1 expression in human HCC cells
CCL2 is a major chemo-attractant for macrophages
Macrophage infiltration promotes tumor metastasis

Hypothesis:
Whether FoxC1-induced CCL2 secretion promotes macrophage infiltration and HCC metastasis.
FoxC1 expression in HCC cells promoted macrophage attraction through the CXCR1/CCL2 axis

BMDMs
FoxC1 promotes macrophage infiltration and HCC metastasis through up-regulating CXCR1 and CCL2 expression.
Depletion of macrophages decreased FoxC1-mediated HCC metastasis.
FoxC1 expression is positively correlated with IL-8, CXCR1, CCL2 expression and intratumoral TAM infiltration

Correlation analysis of FoxC1 expression and IL-8, CXCR1, CCL2 expression or TAM infiltration in 690 human HCC tissues

<table>
<thead>
<tr>
<th></th>
<th>FoxC1 negative (n=308)</th>
<th>FoxC1 positive (n=382)</th>
<th>P value</th>
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<tr>
<td>IL-8</td>
<td>185</td>
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<td>CXCR1</td>
<td>173</td>
<td>152</td>
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<tr>
<td>CCL2</td>
<td>205</td>
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<td></td>
<td>102</td>
<td>257</td>
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<tr>
<td>TAM</td>
<td>191</td>
<td>138</td>
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<td></td>
<td>117</td>
<td>244</td>
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</table>
FoxC1(+)/CCL2(+) or FoxC1(+)/TAM(+) were associated with poorer prognosis.
FoxC1 can be used as a prognostic marker, and targeting CCL2 and macrophage infiltration can be used to develop a better treatment for patients with HCC.
Acknowledgement

Lab members in Xijing Hospital of Digestive Diseases

Limin Xia  Feng Du  Yunzhi Dang  Jing Ma  Hao Liu  Jie Chen  Weibo Feng  Meirui Qian

Funding

• National Natural Science Foundation of China (No.81522031, No. 81772623, No. 81627807, No.81430072 and No. 81421003)
• National Key Research and Development Program of China (2018YFC1312103)
• National Center for Clinical Research of Digestive Diseases (2015BAI13B07)
Joint committee consensus on the management of primary retroperitoneal soft tissue sarcomas from CPAM, CACA and CMA

October 3, 2018  Kuala Lumpur

2018 World Cancer Congress

Chunyi Hao, M.D.
Sarcoma Center, Peking University Cancer Hospital
Specific features of the disease:

- Oncologically: location, size, heterogeneity……
- Medically: academic, technique, team, facilities, paradigms……
- Scientifically: meet the demands of precision medicine

Over 10 guidelines existed already:

- NCCN, ESMO, SEOM, trans-Atlantic……But……
Principles for the consensus

EBM

nationally adapted

scientificity

universality

advancement

sustainable development
Contents

1. Preface: background + definition
   • definition: soft tissue sarcoma, retroperitoneal space, retroperitoneal tumor
   • not-included tumors: GISTs, metastatic

2. Consensus formation: expert committee + literature review

3. Consensus body:
   ① Diagnosis
   ② Surgery
   ③ Interventional therapy
   ④ Systemic therapy
   ⑤ Establishment of MDT
   ⑥ Data collection and follow-ups

4. Epilogue: evaluation, usage, update, interest conflict and copyright
### Grading of evidence & strength of recommendations

<table>
<thead>
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<th>Grading of evidence</th>
<th>Strength of recommendations</th>
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<td><strong>A</strong> (high)</td>
<td>1: <strong>strong</strong></td>
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<tr>
<td>Further research is unlikely to change our confidence in the estimate of effect.</td>
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<tr>
<td><strong>B</strong> (moderate)</td>
<td>2: <strong>general</strong></td>
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<td>Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.</td>
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<tr>
<td><strong>C</strong> (low)</td>
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<tr>
<td>Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.</td>
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Radiologic diagnosis

The goal of RD before, during and after the treatment:

1. To know the tumor texture and the internal consistence, size, number, location, scope and correlation with neighboring structures, and possible histopathologic types, facilitating the differential diagnosis, staging, prognostic evaluation and individualized therapy making;

2. To know the possible existence of distant metastases, and the location, scope, number and size of the metastatic lesions;

3. To evaluate the efficacy of treatment, facilitating the adjustment basis;

4. To evaluate the surgical risk and contraindications for candidate patients;

5. For possible kidney resection patient, to evaluate the shape, function and possible vascular involvement of the contralateral kidney;

6. Follow-ups.
Our recommendations:

① For initially resectable tumors, unless enrolled in clinical trials, or could not exclude the diseases such as lymphoma, Ewing’s sarcoma, GIST or metastatic tumors which surgery is usually not the primary choice, preoperative biopsy is not necessitated;

② For initially unresectable tumors, whether primary or metastatic, pretreatment biopsy is mandatory to facilitate bases for further treatment.

Considering the potential risk of needle tract seeding, we recommend limiting the needle biopsy to those who will not accept curable treatment:

Biopsy methods:

Laparotomy, laparoscope, fine-needle/core-needle aspiration
Surgery

General comment: the mainstay for retroperitoneal tumors, and the only potentially curable modality

1. Basic considerations
   • Prognostic factors
   • Principals of surgery
   • Marginal evaluation and surgical scope
   • Partial resection

2. Locally recurrent tumors
   • Resectability
   • Timing for surgical intervention

3. Distant metastases

4. The position of minimally invasive surgery

5. Adjuvant, neo-adjuvant and intraoperative radiation
General considerations in Surgery (I)

1-prognostic factors

1. High risk factors for local recurrence, distant metastases and tumor-related death
2. Tumor size and histologic grading (AJCC)
3. Location, histologic type and marginal status (R0?)
4. The volume and management paradigm that medical institutes treat such diseases

2-principle of surgery

R0 resection within the indications and safety
3-evaluation of surgical margin and scope (decided by the operator)

• Evaluation of surgical margin: high difficulty and low precision
• Surgical scope: decided by operator based on his experience and academic concept (pre-and-intra operative)

Recommendation:

For all the first time surgeries in resectable retroperitoneal sarcomas, extended en block resections should be performed on the premise of safety. For those extended resections could not be performed because of specific locations, intra- or post-operative radiation should be considered.
A CASE for SHARING

Extended resections for retroperitoneal sarcomas
Right primary retroperitoneal sarcoma, extended resection of the right kidney, colon
Together with the Whipple procedure
Resection and replacement of IVC...
Partial (palliative) resections

Generally, partial resection will not significantly improve the survival, but……

Recommendations:

For unresectable patients, the feasibility of palliative resection should be discussed through MDT. Individualized management should be made based on the aspects of tumor, patient, medical facilities, etc.
Management of local recurrences (I)

Resectability evaluations (technically, biologically and socio-economically)

General condition, medical imaging, previous surgeries, recurrent interval, pathologic grading and actual biologic behavior (e.g. growth speed, metastases, etc), even the social-economic status and demands should all be considered.
Timing for surgery in local recurrences

Unlike the 1st surgery, most local recurrences don’t need immediate resections:

1. For those in specific location, where further growing will bring unresectability, immediate surgery is warranted;
2. For most others, close follow-ups could be made and selective surgery should be performed based on relevant considerations;
3. Biologically, for those with high pathologic grading, short recurrent interval and fast growing features, close follow-up should be made to avoid unfeasible surgical intervention.
### Other contents in the consensus

<table>
<thead>
<tr>
<th>Management of distant metastases</th>
<th>Systemic therapy</th>
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<tbody>
<tr>
<td>Position of minimally invasive surgery</td>
<td>Structure and establishment of MDT</td>
</tr>
<tr>
<td>Pre-, intra- and post-operative radiation</td>
<td>Data-collection and follow-ups</td>
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<tr>
<td>Position and role of interventional radiology</td>
<td>Interest conflict disclosure and copyright</td>
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</table>
Thank for your kind listening! and
looking forward to your comments & suggestions

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haochunyi@vip.sina.com
Surgical Treatment of the Primary Tumor in Patients With De Novo Stage IV Breast Cancer

Zhengkui Sun, MD. Jiangxi Cancer Hospital
A CASE

- A patient with left breast cancer with metastatic disease in the ipsilateral axilla, Internal mammary and mediastinum at the age of 49. Grade II invasive ductal carcinoma, ER-, PR-, Her-2 positive and Ki67-70%, treated initially with chemotherapy of epirubicin and docetaxol, in addition to trastuzumab.
- At 4 months after initiation of therapy, complete response was achieved in axilla, Internal mammary, and mediastinum. Partial response was achieved in breast.
- Should she receive locoregional surgical treatment?
- In our hospital, 281 (8.4%), of 3,356 breast cancer patients at diagnoses were de novo stage IV from 2013 to 2018.
De Novo Stage IV Breast Cancer

- Globally, breast cancer is the most common cancer diagnosis in female. Approximately 6% of breast cancer patients were diagnosed de novo stage IV disease.
- It is estimated that in 2017 approximately 155,000 women have stage IV breast cancer in the United States, one-quarter of whom were diagnosed with de novo stage IV disease.

CA Cancer J Clin 2018;1-30;
• The primary treatment approach recommended by the NCCN Panel for women with metastatic breast cancer and an intact primary tumor is systemic therapy.

• Surgery after initial systemic treatment is considered for those women requiring palliation of symptoms or with impending complications, such as skin ulceration, bleeding, fungation, and pain.

• Generally surgery should be undertaken only if complete local clearance of tumor may be obtained and if other sites of disease are not immediately threatening to life.

• Alternatively, radiation therapy may be considered as an option to surgery.
Survival of de novo MBC and recurrent MBC

A retrospective cohort analysis:

- dnMBC should be considered as a separate entity entirely
- 5-year DSS was 44% and 21% for de novo MBC and rMBC (p<0.001)
- 5-year DSS for dnMBC improved over time from 1990 to 2010
A SEER database analysis: Survival in de novo stage-IV breast cancer

- 7575 patients with de novo stage-IV breast cancer from 2010 to 2013, did experience favorable survival prognosis
- The HR+/HER2+ disease was associated with the best prognosis, HR+/HER2– and HR–/HER2+ disease was associated with the better prognosis, whereas HR–/HER2– subtype was associated with a significantly poorer outcome
- In the multivariate analyses, patients with bone-only metastases did experience best survival prognosis, whereas patients with liver and brain metastases were significantly unfavorable prognosis
The purpose of the treatment for advanced breast cancer

- To prolong survival time of patients: Systemic therapy ↑ Local therapy ?
- To relieve symptoms: Systemic/Local therapy↑
- To improve the quality of life of the patients: Systemic/Local therapy↑
Prospective studies: Surgical excision of the primary tumor

<table>
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<tr>
<th>studies</th>
<th>recruitment</th>
<th>patients recruited</th>
<th>Systemic therapy before randomisation</th>
<th>primary end point</th>
<th>outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBCRC 013 trial</td>
<td>2009-12</td>
<td>112</td>
<td>yes</td>
<td>survival</td>
<td>negative</td>
</tr>
<tr>
<td>India</td>
<td>2005-12</td>
<td>350</td>
<td>yes</td>
<td>survival</td>
<td>negative</td>
</tr>
<tr>
<td>Turkey</td>
<td>2008-12</td>
<td>271</td>
<td>no</td>
<td>survival</td>
<td>positive</td>
</tr>
<tr>
<td>USA and Canada</td>
<td>2011-15</td>
<td>368</td>
<td>yes</td>
<td>survival</td>
<td>---</td>
</tr>
<tr>
<td>Danish</td>
<td>2011-16</td>
<td>516</td>
<td>yes</td>
<td>survival</td>
<td>---</td>
</tr>
<tr>
<td>Japan</td>
<td>2011-16</td>
<td>500</td>
<td>yes</td>
<td>survival</td>
<td>---</td>
</tr>
<tr>
<td>Austria</td>
<td>2010-19</td>
<td>254</td>
<td>no→yes</td>
<td>survival</td>
<td>---</td>
</tr>
</tbody>
</table>

2016 ASCO Annual Meeting, 2017 ASCO Annual Meeting
Cohort B: 15 patients with metastatic within 3 mos of primary surgery

Cohort A: 112 patients with de novo stage IV breast cancer

Systemic treatment

Responders 94 (85%)
Non-responders 17 (15%)

elective Surgery 39 (43%)
no surgery 51 (57%)

To compare cohorts A and B and within cohort A stratified by response to systemic therapy

To compare 3yr-OS between surgery of the primary tumor and no surgery using log rank, Kaplan Meier, and Cox regression

Presented By Tari King at 2016 ASCO Annual Meeting
TBCRC 013 trial

Survival by ER/Her2 and surgery

Multivariate analysis for OS

<table>
<thead>
<tr>
<th>Responders</th>
<th>Surgery</th>
<th>N</th>
<th>Median Survival, mos</th>
<th>3yrOS (95%CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+HER2+</td>
<td>N</td>
<td>8</td>
<td>NR (NR-NR)</td>
<td>88% (67-100)</td>
<td>0.07</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>12</td>
<td>77 mos (77-NR)</td>
<td>100% (100-100)</td>
<td></td>
</tr>
<tr>
<td>ER+HER2-</td>
<td>N</td>
<td>38</td>
<td>71 mos (49-NR)</td>
<td>76% (64-91)</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>22</td>
<td>53 mos (51-NR)</td>
<td>68% (51-91)</td>
<td></td>
</tr>
<tr>
<td>ER-HER2+</td>
<td>N</td>
<td>4</td>
<td>NR (24-NR)</td>
<td>75% (43-100)</td>
<td>0.51</td>
</tr>
<tr>
<td></td>
<td>Y</td>
<td>3</td>
<td>47 mos (38-NR)</td>
<td>100% (100-100)</td>
<td></td>
</tr>
</tbody>
</table>

Presented By Tari King at 2016 ASCO Annual Meeting
Tata Memorial trial, India

716 patients presented with metastatic disease

691 eligible for systemic chemotherapy

276 non-responders

415 responders and eligible for study

25 eligible for endocrine therapy

440 registered for study

90 not eligible for surgery or declined to participate

350 patients randomly assigned

173 to receive locoregional treatment

173 to receive no locoregional treatment

Primary endpoint: OS
Outcome: There was no difference in overall survival between the two groups

Lancet Oncol 2015
Locoregional treatment resulted in a significant improvement in locoregional progression-free survival. HR 0.16, 95% CI 0.10–0.26; p<0.0001.

Locoregional treatment resulted in a significant detriment in distant progression-free survival. HR 1.42, 95% CI 1.08–1.85; p=0.012.
Turkey MF07-01

Enrolled 274 patients with de novo stage IV BC randomly assigned

136 in the ST group

138 in the LRT group

Systemic therapy

Primary aim: OS
Second aim: RLP

Results: secondary end points

<table>
<thead>
<tr>
<th></th>
<th>Surgery</th>
<th>ST</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>locoregional progression/relapse</td>
<td>1% (2)</td>
<td>11% (15)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

- The rate of LPR was lower in the LRT group than in the ST (p = 0.001)

Ann Surg Oncol 2018
Survival improvement in 36-month was not observed

A follow-up study in 60 months showed statistically significant survival improvement in the LRT group, Hazard of death was 34% lower (HR, 0.66; 95% CI, 0.49–0.88; p=0.005)
Turkey MF07-01: Subgroup analyses:

The risk of death was statistically lower in the LRT group than in the ST group with respect to:

- ER/PR (+): p=0.01
- HER2(–): p=0.01
- Patients younger than 55 years: p = 0.007)
- Patients with solitary bone-only metastases: p=0.04
Meta-Analysis: Surgery of primary tumors in stage IV BC

- A pooled hazard ratio is 0.63 (P<0.0001) from 16 retrospective case studies.
- It was concluded that surgery of the primary tumor in stage IV breast cancer appears to offer a survival benefit.
- But this selection bias is likely to contribute substantially to the survival advantage.

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>log[Hazard Ratio]</th>
<th>SE</th>
<th>Total</th>
<th>Total</th>
<th>Weight</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Akay CL et al 2014</td>
<td>-1.38629</td>
<td>0.581344</td>
<td>79</td>
<td>93</td>
<td>0.7%</td>
<td>0.25 [0.08, 0.78]</td>
</tr>
<tr>
<td>Babiera GV et al 2006</td>
<td>-0.9315</td>
<td>0.442602</td>
<td>82</td>
<td>142</td>
<td>1.2%</td>
<td>0.50 [0.21, 1.19]</td>
</tr>
<tr>
<td>Bafford AC et al 2009</td>
<td>-0.75502</td>
<td>0.25446</td>
<td>61</td>
<td>86</td>
<td>3.0%</td>
<td>0.47 [0.29, 0.77]</td>
</tr>
<tr>
<td>Blanchard DK et al 2008</td>
<td>-0.34249</td>
<td>0.124743</td>
<td>242</td>
<td>153</td>
<td>7.6%</td>
<td>0.71 [0.56, 0.91]</td>
</tr>
<tr>
<td>Dominici L et al 2011</td>
<td>-0.06188</td>
<td>0.057387</td>
<td>54</td>
<td>236</td>
<td>12.2%</td>
<td>0.94 [0.84, 1.05]</td>
</tr>
<tr>
<td>Fielder RC et al 2007</td>
<td>-0.63488</td>
<td>0.118685</td>
<td>187</td>
<td>222</td>
<td>7.9%</td>
<td>0.53 [0.42, 0.67]</td>
</tr>
<tr>
<td>Onerlich J et al 2007</td>
<td>-0.46204</td>
<td>0.024893</td>
<td>4575</td>
<td>5159</td>
<td>14.0%</td>
<td>0.63 [0.60, 0.66]</td>
</tr>
<tr>
<td>Hazard HW et al 2008</td>
<td>-0.22565</td>
<td>0.352369</td>
<td>47</td>
<td>64</td>
<td>1.7%</td>
<td>0.80 [0.40, 1.59]</td>
</tr>
<tr>
<td>Khan SA et al 2002</td>
<td>-0.4943</td>
<td>0.22573</td>
<td>9162</td>
<td>6661</td>
<td>14.0%</td>
<td>0.61 [0.58, 0.64]</td>
</tr>
<tr>
<td>Lang JE et al 2013</td>
<td>-0.52763</td>
<td>0.266423</td>
<td>74</td>
<td>134</td>
<td>2.8%</td>
<td>0.59 [0.35, 0.99]</td>
</tr>
<tr>
<td>Neuman HB et al 2010</td>
<td>-0.34249</td>
<td>0.210476</td>
<td>69</td>
<td>117</td>
<td>4.0%</td>
<td>0.71 [0.47, 1.07]</td>
</tr>
<tr>
<td>Pathy NB et al 2011</td>
<td>-0.54473</td>
<td>0.096552</td>
<td>139</td>
<td>236</td>
<td>9.4%</td>
<td>0.58 [0.48, 0.70]</td>
</tr>
<tr>
<td>Perez-Fidalgo JA et al 2011</td>
<td>-0.95393</td>
<td>0.201988</td>
<td>123</td>
<td>85</td>
<td>4.3%</td>
<td>0.52 [0.35, 0.77]</td>
</tr>
<tr>
<td>Rapiti E et al 2006</td>
<td>-0.51083</td>
<td>0.20687</td>
<td>127</td>
<td>173</td>
<td>4.1%</td>
<td>0.60 [0.40, 0.90]</td>
</tr>
<tr>
<td>Rashaan ZM et al 2011</td>
<td>-0.51083</td>
<td>0.20687</td>
<td>127</td>
<td>173</td>
<td>4.1%</td>
<td>0.60 [0.40, 0.90]</td>
</tr>
<tr>
<td>Ruiterkamp J et al 2009</td>
<td>-0.47804</td>
<td>0.099647</td>
<td>268</td>
<td>440</td>
<td>9.1%</td>
<td>0.82 [0.51, 0.75]</td>
</tr>
</tbody>
</table>

Total (95% CI): 15368

Heterogeneity: Tau² = 0.02; Ch² = 59.43, df = 15 (P = 0.00001); I² = 75%
Test for overall effect: Z = 9.18 (P < 0.00001)
Matched Pair Analyses of Stage IV BC with or Without Resection of Primary Breast Site

- 622 patients from Massachusetts General Hospital (MGH) and the Brigham Women’s Hospital (BWH)
- Case-matching compared patients with and without primary site surgery by age, date of diagnosis, location of metastatic disease, estrogen receptor status, and use of systemic therapy
- Separate Kaplan–Meier curves are shown survival benefit of patients who received primary site surgery in all (n = 464) and case-matched group (n = 304)

Annals of Surgical Oncology 15(12):3384–3395
Matched Pair Analyses of Stage IV BC with or Without Resection of Primary Breast Site

Separate Kaplan–Meier curves are shown survival benefit of patients who received primary site surgery than those who received no surgery in all bone metastases (n = 255) and in case-matched within the subset (n = 168).

Annals of Surgical Oncology 15(12):3384–3395
Matched Pair Analyses of Stage IV BC with or Without Resection of Primary Breast Site

Separate Kaplan–Meier curves are shown survival benefit of patients who received primary site surgery in all visceral metastases (n = 159) and no survival benefit of patients in case-matched group within the subset (n = 100)

Annals of Surgical Oncology 15(12):3384–3395
Locoregional therapy in breast cancer subtypes with de novo stage IV disease

- Local treatments (surgery and/or radiotherapy) to primary tumors achieved better survival in patients with luminal-like and HER2-enriched subtypes, but not in triple negative subtype
- De Novo Stage IV breast cancer patients with luminal-like or HER2-enriched subtype should be offered local treatments

3-year survival: 66.4% vs. 34.4%, p=0.0001
3-year survival: 41.6% vs. 8.8%, p=0.0012
3-year survival: 6.7% vs. 14.8%, P=0.9575

246 patients From 1990 to 2009 in Sun Yat-Sen Cancer Center, Taiwan
Conclusions

• The potential role of surgical resection of the primary tumor for improving outcomes remains a subject of debate

• The prospective studies did not demonstrate a favorable impact of local surgery on survival, but did show better local disease control. but the small size of the study is a significant limitation

• Retrospective studies generally support a survival advantage from local surgery but are prone to significant bias. Matched pair analyses shown case selection bias may not explain all the apparent survival advantage

• Patients who fall into this group may reach significant long-term survival should be consider local surgery therapy

• It appears logical to consider local therapy for the primary tumor if all sites of distant disease are well-controlled, but the primary site continues to progress
THANK YOU!
Curability of Radiotherapy in Elderly Patients with Early-stage Extranodal Nasal-type NK/T-cell Lymphoma: A Multicenter Study

Suyu Zhu, M.D.

Hunan Cancer Hospital
the Affiliated Cancer Hospital of Xiangya School of Medicine,
Changsha, Hunan, P. R. China
On behalf of the China Lymphoma Collaborative Group (CLCG)
1. Extranodal nasal-type NK/T-cell lymphoma (NKTCL) is common in China and East Asia, but is rare in Western countries.

Radiotherapy is essential to the treatment for early-stage NKTCL, with 5-year overall survival (OS) rates between 70% and 90%.

Before Radiotherapy

After Radiotherapy
1. Age > 60 years is an independent adverse factor for NKTCL.

2. High frequency of comorbidities and diminished organ function in older patients would affect their treatment safety and efficacy.

3. A few single-institution data series had been reported in literature and larger multi-center study data are needed to further clarify issues related to treatment and prognostication for the elderly patients.
Purpose

1) To determine the curability of radiotherapy in elderly patients with early-stage NKTCL.

2) To determine the potential benefit of new regimen chemotherapy in elderly patients with early-stage NKTCL.
Patient eligibility and treatment

China Lymphoma Collaborative Group NKTCL program data pool 2640 cases

(1) patient age more than 60 years;
(2) stage I and II disease;
(3) treatment with curative intent.

321 cases

Received RT 262 cases

Received CT 234 cases

RT alone 87 cases
RT + CT 175 cases
CT alone 59 cases

New CT regimen 122 cases
Old CT regimen 112 cases
## Patients characteristics and univariate analysis

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. (%)</th>
<th>5-year OS</th>
<th>p</th>
<th>5-year PFS</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>%</td>
<td></td>
<td>%</td>
<td></td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>249 (77.6)</td>
<td>55.7</td>
<td>0.211</td>
<td>50.2</td>
<td>0.293</td>
</tr>
<tr>
<td>Female</td>
<td>72 (22.4)</td>
<td>67.2</td>
<td>0.211</td>
<td>58.1</td>
<td>0.293</td>
</tr>
<tr>
<td><strong>B symptoms</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>229 (71.3)</td>
<td>60.6</td>
<td>0.069</td>
<td>54.4</td>
<td>0.100</td>
</tr>
<tr>
<td>Yes</td>
<td>72 (22.4)</td>
<td>51.7</td>
<td>0.069</td>
<td>45.5</td>
<td>0.100</td>
</tr>
<tr>
<td><strong>Elevated LDH</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>232 (72.3)</td>
<td>61.3</td>
<td>0.069</td>
<td>54.9</td>
<td>0.124</td>
</tr>
<tr>
<td>Yes</td>
<td>89 (27.7)</td>
<td>50.1</td>
<td>0.069</td>
<td>45.0</td>
<td>0.124</td>
</tr>
<tr>
<td><strong>ECOG PS</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>292 (91.0)</td>
<td>60.8</td>
<td>0.002</td>
<td>54.0</td>
<td>0.001</td>
</tr>
<tr>
<td>≥ 2</td>
<td>29 (9.0)</td>
<td>34.7</td>
<td>0.002</td>
<td>32.9</td>
<td>0.001</td>
</tr>
<tr>
<td><strong>PTI</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absence</td>
<td>154 (48.0)</td>
<td>72.7</td>
<td>&lt;0.001</td>
<td>63.7</td>
<td>0.005</td>
</tr>
<tr>
<td>Presence</td>
<td>167 (52.0)</td>
<td>44.5</td>
<td>&lt;0.001</td>
<td>40.9</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Ann Arbor Stage</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>I</td>
<td>228 (71.0)</td>
<td>63.3</td>
<td>0.001</td>
<td>54.4</td>
<td>0.005</td>
</tr>
<tr>
<td>II</td>
<td>93 (29.0)</td>
<td>44.6</td>
<td>0.001</td>
<td>47.8</td>
<td>0.005</td>
</tr>
<tr>
<td><strong>Risk group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 (low-risk)</td>
<td>99 (30.8)</td>
<td>80.0</td>
<td>&lt;0.001</td>
<td>71.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥ 1 (high-risk)</td>
<td>222 (69.2)</td>
<td>47.9</td>
<td>&lt;0.001</td>
<td>43.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

### Summary:
- Median age: 66y; 68.2% < 70y;
- Male/Female: 3.5/1
- Stage I: 71%
- Good PS: 91%
- PTI: 52%
- Elevated LDH: <30%
- B symptoms: <30%

### univariate analysis:
- PS, PTI, and stage significantly influenced OS and PFS.
Results: OS and PFS stratified on risk factors

Risk stratification: nomogram model

Age-adjusted Risk factors:
ECOG score ≥ 2;
stage II;
elevated LDH;
PTI;

Low-risk: 0 risk factor (n = 99);
High-risk: ≥ 1 risk factor (n = 222);

RT received (n = 262)
5-year OS and PFS: 82.2% and 74.4% in the low-risk (n = 87)
50.4% and 47.5% in the high-risk (n = 175)
Results: Radiotherapy versus Chemotherapy alone

- 5-y: 61.2%
- 5-y: 44.7%
- 5-y: 56.4%
- 5-y: 38.3%
- 5-y: 52.5%
- 5-y: 44.7%
- 5-y: 50.2%
- 5-y: 38.3%
Results: RT alone versus RT + CT

<table>
<thead>
<tr>
<th></th>
<th>RT (n = 57)</th>
<th>RT + CT (n = 175)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-y OS</td>
<td>66.9%</td>
<td>58.1%</td>
<td>0.463</td>
</tr>
<tr>
<td>5-y PFS</td>
<td>62.8%</td>
<td>53%</td>
<td>0.570</td>
</tr>
</tbody>
</table>
Results: Survival benefit of new chemotherapy regimens

A
- 5-y: 71.9%
- 5-y: 51.3%

CMT with new regimen (n = 86)
CMT with old regimen (n = 89)
P = 0.075

B
- 5-y: 71.2%
- 5-y: 44.2%

CMT with new regimen (n = 86)
CMT with old regimen (n = 89)
P = 0.017
Results: comparison with the general population (Risk-dependent curability in response to radiotherapy)

SMR: 0.703

Low-risk group

Low-risk group

SMR: 3.191

High-risk group

SMR: 1.867

High-risk group

SMR: 1.490

High-risk group
Results: death and safety

With the median follow-up of 42 months for living patients:

114 patients (35.5%) had died;

93 patients (29.0%) related to lymphoma,

13 (4.0%) related to other diseases,

8 (2.5%) from chemotherapy-related toxicities.

No patients died of radiotherapy-related toxicities or developed second neoplasms.
Conclusion:

1) Radiotherapy achieves a favorable outcome for elderly patients with early-stage NKTCL.

2) New chemotherapy regimen and radiotherapy significantly improved PFS compared with the old chemotherapy regimen and radiotherapy.

3) Low-risk patients at treatment and high-risk patients that are PFS at 24 months show a subsequent OS equivalent to the general Chinese population.

Our findings highlight the curability of radiotherapy and new chemotherapy regimen and provide a risk-adapted follow-up and counsel scheme in this specific population.
China Lymphoma Collaborative Group, CLCL
Abdominal neoplasms and lymphoma section, Radiation Oncology Department, Hunan Cancer Hospital
谢谢
Thanks