Role of Tumor Doubling Time in HCC

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- Tumor growth and cell kinetics
- Tumor doubling time of untreated HCC
- Tumor doubling time relating to treatment of HCC
- Variables related to tumor doubling time in HCC
- Clinical implications of tumor doubling time
- Summary & conclusions
General concept of tumor growth and cell kinetics
Irrespective of their growth rates, most human tumors have been found:

- to start from one single cell,
- to have a long subclinical period,
- to grow at constant rates for long periods of time,
- to start to metastasize often even before the primary is detected,
- to have metastases that often grow at approximately the same rate as the primary tumor.

Monoclonality

- A primary tumor starts from one single cell, in the same way that all human beings originate from a single cell, the fertilized egg.

- The notion that a tumor develops from a single cell (monoclonality) was anticipated by Virchow in 1862.

- Today, monoclonality has been shown for the majority of human tumors.

- Heterogeneous clones are likely to occur later during the lifespan of a tumor.
  - Ample time to diversify during the preclinical period
  - Accumulate genetic changes associated with different or more variable rates of growth.
Mathematical model for tumor growth

- Gompertz curve

- Mobile phone uptake
- Population in a confined space
- Modeling of growth of tumors
Cell kinetics

- Increase in tumor cells -

1 cell -> 2 cells -> 4 cells -> 8 cells -> 16 cells -> 32 cells ->...

✓ Exponential multiplicity with time from the first tumor cell

✓ The curve in this figure gives the impression that a tumor doubles its volume at accelerating speed.

Growth pattern of a tumor

10 μm --> a single cell

Detectable period

Undetectable subclinical period

If the addition to the total tumor burden from the metastases is also included, the curve approaches a straight line.


Growth rate of three different tumors

(1) faster growth rate
(2) identical growth rate
(3) Slower growth rate

Relatively long period of preclinical phase (ex. HCC, adenoca, Lung ca..)

Linearity of increase in volume on a logarithmic scale has been observed for several types of human malignancies.

In many instances, linearity has been maintained during several years and with numerous observations.

- Ex. Breast ca FU with $\geq$ 5 times for 3-9 yrs -

Fournier D, et al. Cancer 1980;45:2198,

Numerous examples of cases --> displaying linear growth
Growth rate --> expressed as tumor doubling time, as proposed by Collins.

Calculation of tumor volume (formula):

- $4/3\pi r^3$ for spherical nodules,
- $4/3\pi\left(a/2 + b/2\right)^3$ for nonspherical nodules

The formula developed by Schwartz:

$$\text{Tumor doubling time} = \frac{t \times \log 2}{\log V_1 - \log V_0}$$

$t = \text{the time interval between measurements}$
$V_0 = \text{the tumor volumes at the beginning of the time interval}$
$V_1 = \text{the tumor volumes at the end of the time interval}$

## Three groups according to tumor doubling time

<table>
<thead>
<tr>
<th>Group</th>
<th>Tumor doubling time</th>
<th>Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rapid growing group</td>
<td>&lt; 30 days</td>
<td>Ewing’s sarcoma, Testicular carcinoma, Non-Hodgkin’s Lymphoma, Wilms’ tumor</td>
</tr>
<tr>
<td>Intermediate group</td>
<td>30–70 days</td>
<td>Hodgkin’s disease, Osteogenic sarcoma, Fibrosarcoma</td>
</tr>
<tr>
<td>Slow growing group</td>
<td>&gt; 70 days</td>
<td>Most cases of adenocarcinoma, Lung cancer (adenocarcinoma, squamous cell carcinoma, small cell carcinoma), Colon cancer (adenocarcinoma), Prostate cancer, Hepatocellular carcinoma, Breast cancer</td>
</tr>
</tbody>
</table>

Tumor doubling time in HCC
Slow growing tumor of HCC

Time (years)

Number of cells

Clinically detectable status
--> ~32 cell doublings for a volume of 1 cm³

If a TDT of HCC is 150 days

About >12 years
Patterns of growth curves of HCC (I)

- Analysis of 17 untreated HCCs with more than two measurements -

<table>
<thead>
<tr>
<th>Tumor</th>
<th>Proportion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exponential growth</td>
<td>55.6%</td>
</tr>
<tr>
<td>Increased in the later stage</td>
<td>44.4%</td>
</tr>
</tbody>
</table>

Patterns of growth curves of HCC (II)

- Analysis of 17 untreated HCCs with more than two measurements -

Tumor | Proportion
--- | ---
with constant growth rate | 52.9% (9/17)
with declined growth rate | 41.2% (7/17)
with an initial non-growth period | 5.9% (1/17)

# TDT of untreated HCCs

<table>
<thead>
<tr>
<th>References</th>
<th>No of patients</th>
<th>Tumor size (mm)</th>
<th>Doubling time (days)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Mean</td>
<td>Median</td>
</tr>
<tr>
<td>Yoshino M.</td>
<td>13</td>
<td>30 ± 15</td>
<td>119</td>
</tr>
<tr>
<td>Jpn J Clin Oncol (1983)</td>
<td></td>
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<tr>
<td>Sheu JC, et al.</td>
<td>28</td>
<td>23 (&lt; 50)</td>
<td>136</td>
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<tr>
<td>Gastroenterology (1985)</td>
<td></td>
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</tr>
<tr>
<td>Ebara M, et al.</td>
<td>22</td>
<td>&lt; 50</td>
<td>195</td>
</tr>
<tr>
<td>Gastroenterology (1986)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Okazaki N, et al.</td>
<td>15</td>
<td>&lt; 45</td>
<td>102</td>
</tr>
<tr>
<td>Cancer (1989)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barbara L, et al.</td>
<td>39</td>
<td>&lt; 50</td>
<td>204.2</td>
</tr>
<tr>
<td>Hepatology (1992)</td>
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<tr>
<td>Kubota K, et al.</td>
<td>22</td>
<td>&lt; 30</td>
<td>114.9</td>
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<tr>
<td>Taouli B, et al.</td>
<td>11</td>
<td>23–30</td>
<td>127</td>
</tr>
<tr>
<td>J Comput Assist Tomogr (2005)</td>
<td></td>
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</tbody>
</table>
Pooled data from TDT of untreated HCCs

**Averaged TDT**
- 102 ~ 204 days

**Range of TDT**
- 10 ~ 606 days

**Limitations in investigating tumor doubling time in untreated HCCs**
- Analysis of small number of patients (n= <~20)
- Inclusion of at most 40 patients
- All study was done in retrospect.
Accelerated growth rates of recurrent HCC after LT (I)

- TDT for pulmonary metastasis = $44.3 \pm 11.3$ days (range: 10 to 161 days)
- TDT for allograft recurrence = $37.6 \pm 8.9$ days (range: 7 to 65 days)

- No difference in TDT between allograft and pulmonary recurrences
- Fibrolamellar HCC: a greater TDT and a longer survival time than nonfibrolamellar HCC.

Accelerated growth rates of recurrent HCC after LT (II)

TDT after resection
= 273.8 ± 79.1 days (range: 82 to 560 days)

TDT for allograft recurrence
= 37.6 ± 8.9 days (range: 7 to 65 days)

- Recurrent HCCs after LT grow significantly faster than recurrent HCCs after resection

Possible factors involved in this accelerated growth rate:
- the use of immunosuppressive drugs
- the consequent suppression of host immunity against the growth of micrometastasis

Growth rate of recurrent HCC after TACE

Representative case of 79-year-old female patient

- A retrospective analysis of local recurrence after TACE
- CECT scan were measured at least twice.

### Growth rate of recurrent HCC after TACE

<table>
<thead>
<tr>
<th></th>
<th>Primary HCC</th>
<th>Locally recurrent HCC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of nodules</td>
<td>22</td>
<td>60</td>
</tr>
<tr>
<td>Baseline–follow-up vol (mm³)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>605</td>
<td>755</td>
</tr>
<tr>
<td>Range</td>
<td>14.1–14130</td>
<td>11.4–30333</td>
</tr>
<tr>
<td>Follow-up interval (days)</td>
<td></td>
<td></td>
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<tr>
<td>Mean</td>
<td>285</td>
<td>154</td>
</tr>
<tr>
<td>Range</td>
<td>28–1086</td>
<td>25–496</td>
</tr>
<tr>
<td>DT (days)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>83.2</td>
<td>69.7</td>
</tr>
<tr>
<td>Range</td>
<td>34.8–496.4</td>
<td>18.0–412.1</td>
</tr>
<tr>
<td>Geometric mean</td>
<td>87.9</td>
<td>72.9</td>
</tr>
<tr>
<td>95% of lower threshold value</td>
<td>27.3</td>
<td>17.7</td>
</tr>
</tbody>
</table>

- DT at the locally recurrent stage is shorter than that at the primary stage.

Tumor Doubling Time after Complete Remission by Transcatheter Arterial Chemolipiodolization in Patients with Hepatocellular Carcinoma

Woo HY, Choi JY, Yoo CR, Jang JW, Kim CY, Jang WI, Nam SW, Bae SH, Cho SH, Yoon SK, Han JY, Han NY, Choi SW, Lee YS, Lee CD

Department of Internal Medicine, College of Medicine, The Catholic University of Korea, WHO Collaborating Center for Reference and Research on Viral Hepatitis
Patients and Methods

Inclusion criteria (n=184)

New HCC (n=327)

Treatment (n=157)

Conservative or transfer (n=27)

Op (n=14) LT (n=18) RFA (n=4) TACL (n=121)

CR (n=62) No CR (n=59)
Case: tumor doubling time

65/F Patient

Primary HCC

Recurrent HCC

108 days

Recurrent HCC

CR

1.9*1.7 cm

3.4*3.1 cm

Formula by Schwartz: \[
DT = \frac{108 \ln 2}{\ln 191 - \ln 31} = 41 \text{ days}
\]
Tumor Doubling Time after TACE

- Median Doubling Time: 51 days (range 20-240 d)

Factors for short TDT:
- Age $\leq 60$
- Tumor size $> 3.5$ cm
Growth rates of recurrent HCC after RFA

- A retrospective analysis: 62 new HCCs appearing after RFA
- FU CT 1 mo after RFA and then, every 3 months
- Mean TDT: 75 days (median, 61 days; range, 21–209).
- Factors for short TDT: --> HCC size ≤ 1 cm

Variables related to tumor doubling time in HCC
AFP doubling time, HBsAg and TDT

Fig. 4: Correlation between doubling time of tumor volume and level of alpha-fetoprotein (AFP).

Fig. 5: Tumor doubling time (DT) and hepatitis B surface antigen (HBsAg).

Positive correlation between tumor size and doubling time

Small tumors tend to show faster tumor growth.

A mathematic model

Expected TVDT = $114 \times (\text{baseline TV})^{0.14}$

- A retrospective analysis of 16 untreated HCCs in 11 patients with cirrhosis who underwent serial CT or MRI

A retrospective analysis of 34 untreated HCCs

- Well-differentiated type
- Apoptotic index
  - < 3%
  - ≥ 3%
- Ki-67-positive index
  - < 10%
  - ≥ 10%
- Group A
  - Slow growth
  - DT: > 100 days
- Group C
  - Intermediate growth
  - DT: 50-100 days
- Group B
  - Rapid growth
  - DT: < 50 days
- Moderately differentiated type
- Apoptotic index
  - < 3%
  - ≥ 3%
- Ki-67-positive index
  - 10-20%
  - > 20%
- Group D
- Group E

Cell kinetic imbalance

IHC staining for Ki-67 antigen

TUNEL assay

Cell proliferation

Cell death

Growth rate

Intranodular blood supply and TDT

US angiography is performed by intra-arterial injection of CO2 microbubbles into the hepatic artery.

- Hypervascular
- Isovascular
- Hypovascular

US vascular pattern correlates with tumor doubling time.

Postprandial insulin level and TDT
- Analysis of 60 patients (most HCV) with a single HCC < 3 cm -

- AUC(ins) was a significant factor contributing to the growth rate of HCC.
- AUC(ins) significantly decreased after octreotide treatment (p<0.02) but AUC(gluc) did not significantly change.


Postprandial hyperinsulinaemia is associated with accelerated HCC growth.
# Factors related to tumor doubling time

<table>
<thead>
<tr>
<th>References</th>
<th>No of patients</th>
<th>Risk factors identified</th>
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<td>Yoshino M.</td>
<td>13</td>
<td>AFP doubling time, tumor size, presence of HBsAg</td>
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<tr>
<td>Barbara L, et al.</td>
<td>39</td>
<td>Albumin, alcohol intake, tumor number, echo pattern, histological type</td>
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</tr>
<tr>
<td>Nakajima, et al.</td>
<td>34</td>
<td>Ki-67–positive index (Ki-67-Pl), apoptotic index (Apo-I), histological grade.</td>
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<td><em>Hum pathol</em> (2002)</td>
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<tr>
<td>Saito K, et al.</td>
<td>60</td>
<td>Postprandial hyperinsulinaemia</td>
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<td><em>Gut</em> (2002)</td>
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<tr>
<td>Cucchetti A, et al.</td>
<td>62</td>
<td>AFP, microvascular invasion, tumor differentiation</td>
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<tr>
<td><em>J Hepatol</em> (2005)</td>
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<tr>
<td>Kudo M, et al.</td>
<td>52</td>
<td>Intranodular vascular pattern</td>
</tr>
<tr>
<td><em>Oncology</em> (2008)</td>
<td></td>
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</tbody>
</table>
Clinical implications of tumor doubling time of HCC
Pathologic aggressiveness and TDT

- Relevance to cell proliferation marker
  - If TDT ↓ --> Mitotic index ↑, Ki-67-positive index ↑, Apoptotic index ↓

- Relevance to tumor marker
  - If TDT ↓ --> Alpha-fetoprotein doubling time ↓

- Relevance to tumor vascularity
  - If TDT ↓ --> Intra-tumoral vascularity ↑

- Relevance to pathological features
  - If TDT ↓ --> Poor differentiation, Presence of microvascular invasion

Recurrence and TDT

- A retrospective analysis of 62 patients with resection of a single HCC
- In the immediate preoperative, a new US or CT or MR was performed to exclude contraindications to surgery that might have developed during the waiting time.

- DT was the only independent predictor of recurrence (P = 0.005).

An analysis of 15 patients with small HCC < 4.5 cm in diameter. The mean tumor volume doubling time of these 15 nodules was 102 ± 77 days (range 41 to 305 days) before the initiation of a specific treatment for cancer.

There was a significant correlation between TDT and length of survival in medically-treated patients:

\[ Y = 3.8x + 170; \quad r = 0.8812; \quad P < 0.025. \]

Estimation of growth of HCC

Based on the assumption of:
- Linearity of growth
- Constant exponent
- Monoclonality

Screening at 4-5 mo intervals for detecting optimal size (3 cm) treatable with radical Tx

Cancer screening intervals for HCC

- **CT or US screening at 4-monthly intervals for HCC ≤ 2 cm**
  - Based on the shortest TDT = 41 days

- **CECT screening at 3-monthly intervals for HCC of 1-2 cm**
  - Based on the 95% of lower threshold value TDT = 27.1 days

- **CT or MRI screening at 4.5-monthly intervals**
  - Based on the mean TDT = 127 days (4.5 months)

- **US screening at 4 to 5-monthly intervals for HCC ≤ 3 cm**
  - Based on the shortest time = 4.6 months to the detection of 3 cm-sized HCC
Screening intervals for recurrent HCC

- **CECT screening at 2-monthly intervals after TACE**
  - Based on the 95% of lower threshold value TDT = 17.7 days
    

- **Multiphase CT screening at 2.5-monthly intervals for RFA**
  - Based on the mean TDT = 75 days
    
Summary (I)

- **General concept of tumor growth**
  - Monoclonality --> heterogenous clones occur later
  - Long period of preclinical stage
  - Constant exponential growth during the visible stage
  - Growth retardation near at lethal burden

- **General features of tumor doubling time of HCC**
  - Slow growth group
  - Constant exponential growth observed in only 53-56% of HCC

- **Tumor doubling time of untreated HCC**
  - 102–204 days (range: 10-606)
Summary (II)

- **Growth speed after treatment**
  - Accelerated growth speed of recurrent HCC after LT, RFA, and TACE

- **Variables related to faster growth speed in HCC**
  - Short AFP doubling time
  - Poorly differentiated tumor
  - Presence of microvascular invasion
  - Small-sized HCC
  - Presence of HBsAg
  - Multiple tumors
  - Post-prandial hyperinsulinemia
  - Intra-nodular hypervascular pattern on ultrasonographic exam
Various factors affecting tumor growth speed in HCC

- Tumor factors
- Host factors
- Environmental factor
- Viral factors
- Tumor microenvironment
- Treatment
Conclusion

- The assessment of tumor doubling time in HCC patients may provide valuable clinical information on tumor biology, decision of optimal treatment, prognosis, and particularly, screening or monitoring intervals for high-risk patients or after radical treatment.

- Further introduction of additional clinical parameters that reflect the growth rate of HCC may increase the predictive power of the measurement.
Acknowledgement

Special thanks to

동아의대 우현영 교수님
Thank you..
Study limitations in HCC

Tumor factors

Growth speed