

Micrometastases in stomach cancer



Epidemiology

- The incidence of stomach cancer in the world – the fourth disease after lung cancer, breast cancer and colorectal cancer
- The mortality of stomach cancer is still the second – 700 000 new cases annually
- 44 214 patients with stomach cancer were diagnosed in Russia in 2004, 39 708 patients died
- 22 280 patients with stomach cancer and 11 430 deaths have been expected in the USA in 2006

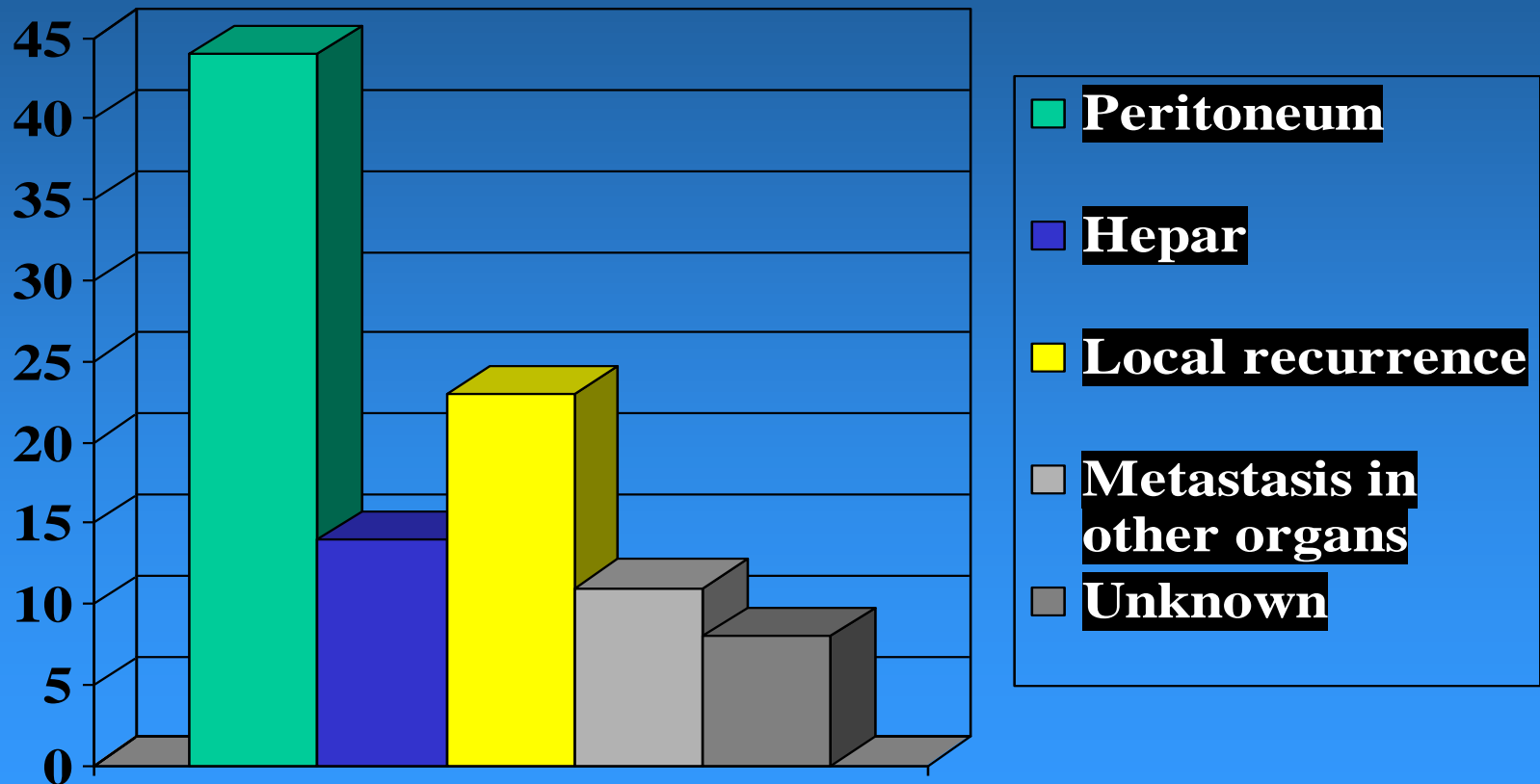
Features of stomach cancer

- The absence of clinical symptoms in early stages
- The rapid dissemination
- Ineffectiveness of chemotherapy and radiotherapy
- The absence of effective screening programs



The incidence of organ recurrences in stomach cancer after surgery

(H.Katai et al., 1994)



Japanese Classification of Gastric Cancer.

- The presence of tumor cells in peritoneal lavage specimens means M1 – stage IV
- The presence of metastasis in bones or in bone marrow means M1 - stage IV
- The presence of cancer cells in blood or micrometastasis in lymph nodes are not mentioned

Definition of micrometastasis

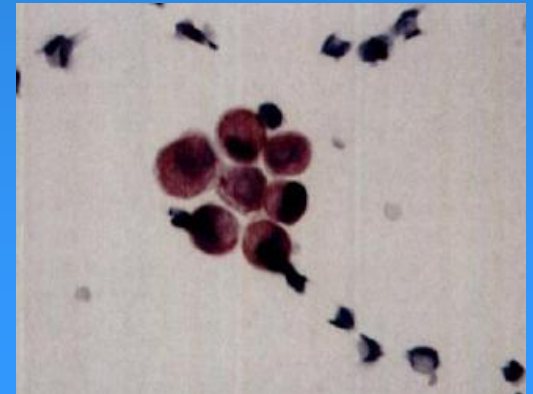
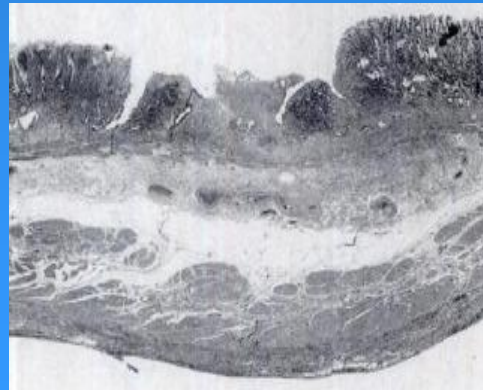
- Micrometastasis was define as a metastatic focus ranging from 0.2 to 2 mm in diameter
- Isolated tumor cell was define as a single tumor cells scattered in the stroma or a small cell cluster < 2 mm in diameter
- Micrometastases – tumor cells which could not be detected by standard histological procedure

The incidence and patterns of recurrence in early stomach cancer

Author, year	The number of patients	The incidence of metastases	The patterns of metastases
Ichiyoshi et al. (1990)	503	17 (3.4%)	9 – hepar, lungs, bones
Sano et al. (1993)	1475	20 (1.4%)	13 (65%) – bones, bone marrow
Lee et al. (2003)	1452	21 (1.4%)	9 – distant metastases
Guadagni et al. (1997)	172	12 (7%)	3- hepar

The incidence of micrometastases in bone marrow in early stomach cancer

- Maehara Y. et al. (1998) – cytokeratin-positive cells in bone marrow were found in 9 (20%) of 45 patients with early stomach cancer
- The neoangiogenesis (CD31 expression) correlated positively with the presence of micrometastases in bone marrow



The incidence of micrometastases in bone marrow in stomach cancer

- Matsunami K. (2003) – 30% (VEGF, HER2 expression did not correlated with the presence of micrometastasis)
- Maehara Y. (1996) – 32.6%
- Jauch KW (1996) – 53%
- Dao-Rong Wang (2006) – 86.9%
- The distant metastases were diagnosed significantly more often in patients with bone marrow micrometastasis

The incidence of bone metastasis in stomach cancer – bone scanning (Choi et al. 1995)

- Bone metastasis were diagnosed in 106 (45.3%) of 234 patients
- Spine – 66%
- Ribs– 59%
- Pelvis – 43%
- Femur – 30%
- Scull – 22%.
- Comments :bone metastasis are not diagnosed in clinical practice

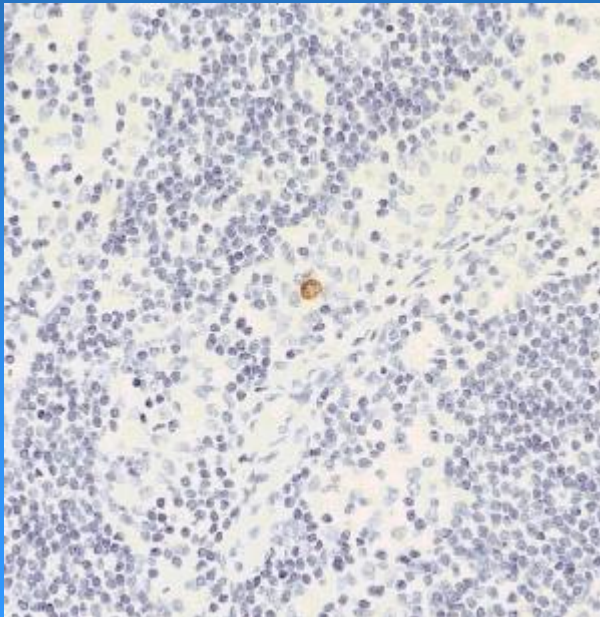
The incidence of micrometastasis in blood.

- X.Chen (2004) – 53%
- D.Wang (2006) – 84%
- Tani N (2007) – 15%
- Xu W (2005) – 38.9%
- Zhang XW (2003) - 42.6% (portal vein – 85.1%)

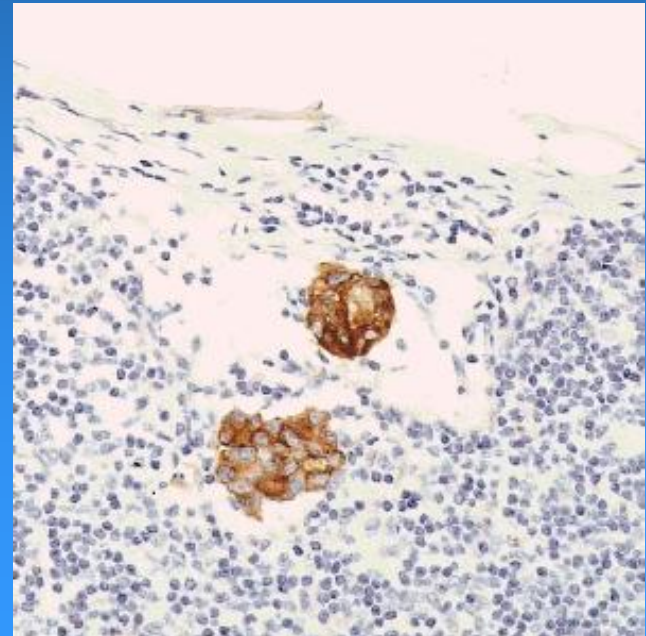
The patterns of lymph node micrometastasis.

(T.Fukagawa et al.Immunohistochemically Detected Micrometastasis of Lymph Nodes in Patients with Gastric Cancer. Aug, 15. 2001 (Vol.92) Number 4, p.753-759)

- Single cell



- Cluster cells

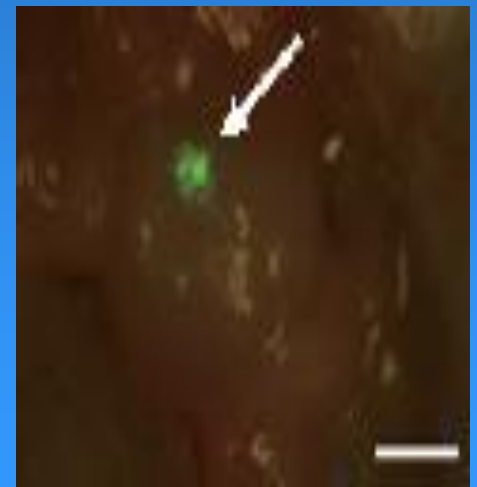
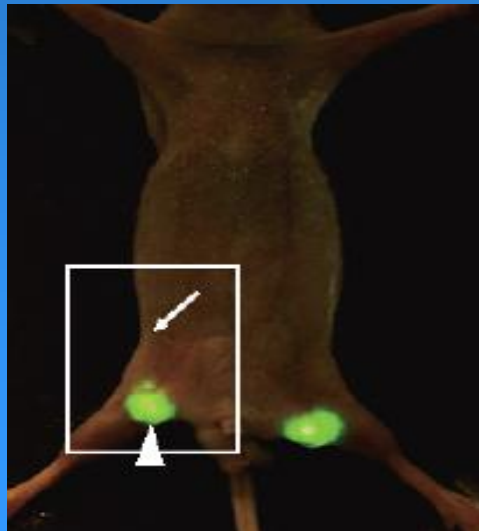


The significance of lymph node micrometastasis in T2N0M0 stage (T.Fukagawa et al., 2001)

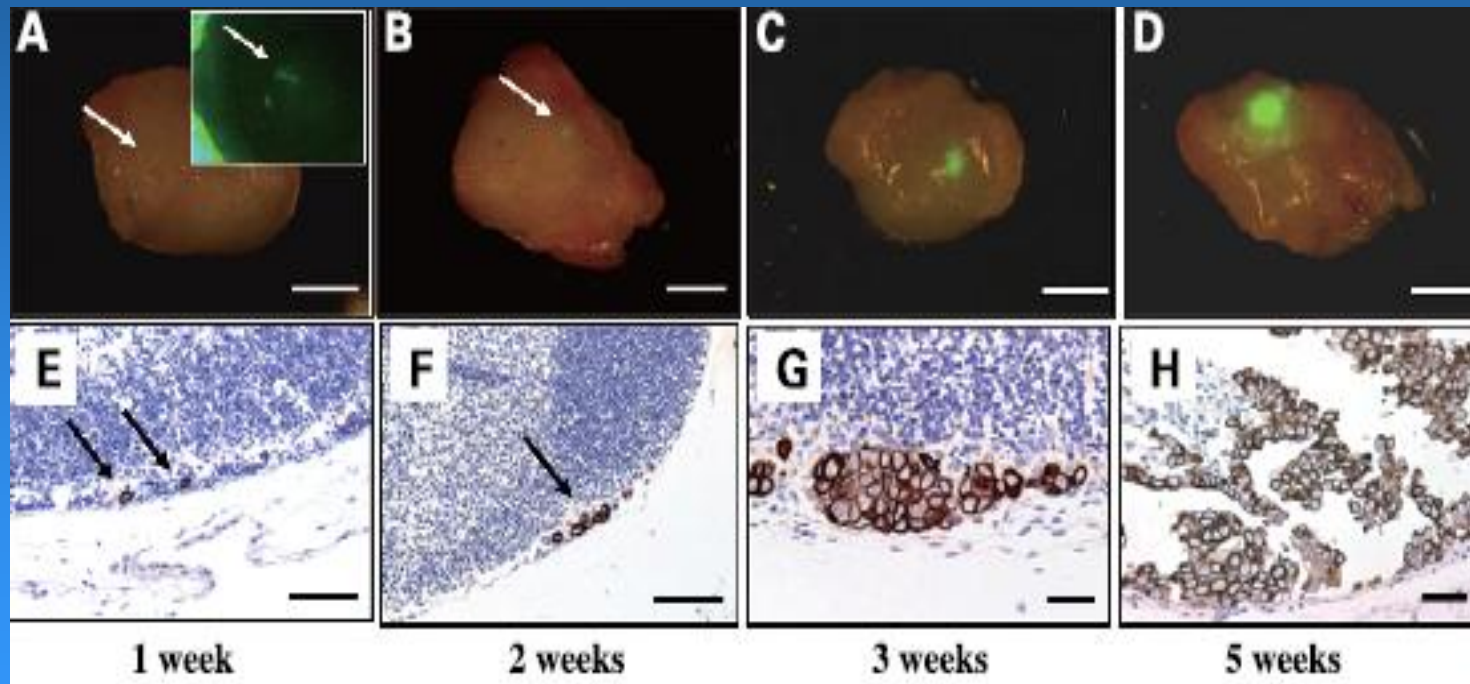
- Micrometastases were diagnosed in 38 (35.5%) of 107 patients with T2N0M0 stage
- D2 lymph node dissection was performed
- There were no differences in 5 and 10 year survival

Single tumor cells and micrometastases in lymph nodes – biological significance. (H.Yokoyama et al. Biological significance of isolated tumor cells and micrometastasis in lymph nodes evaluated using a green fluorescent protein – tagged human gastric cancer cell line. Clin Cancer Res. 2006; 12(2) Jan 15, 2006, p.361-368)

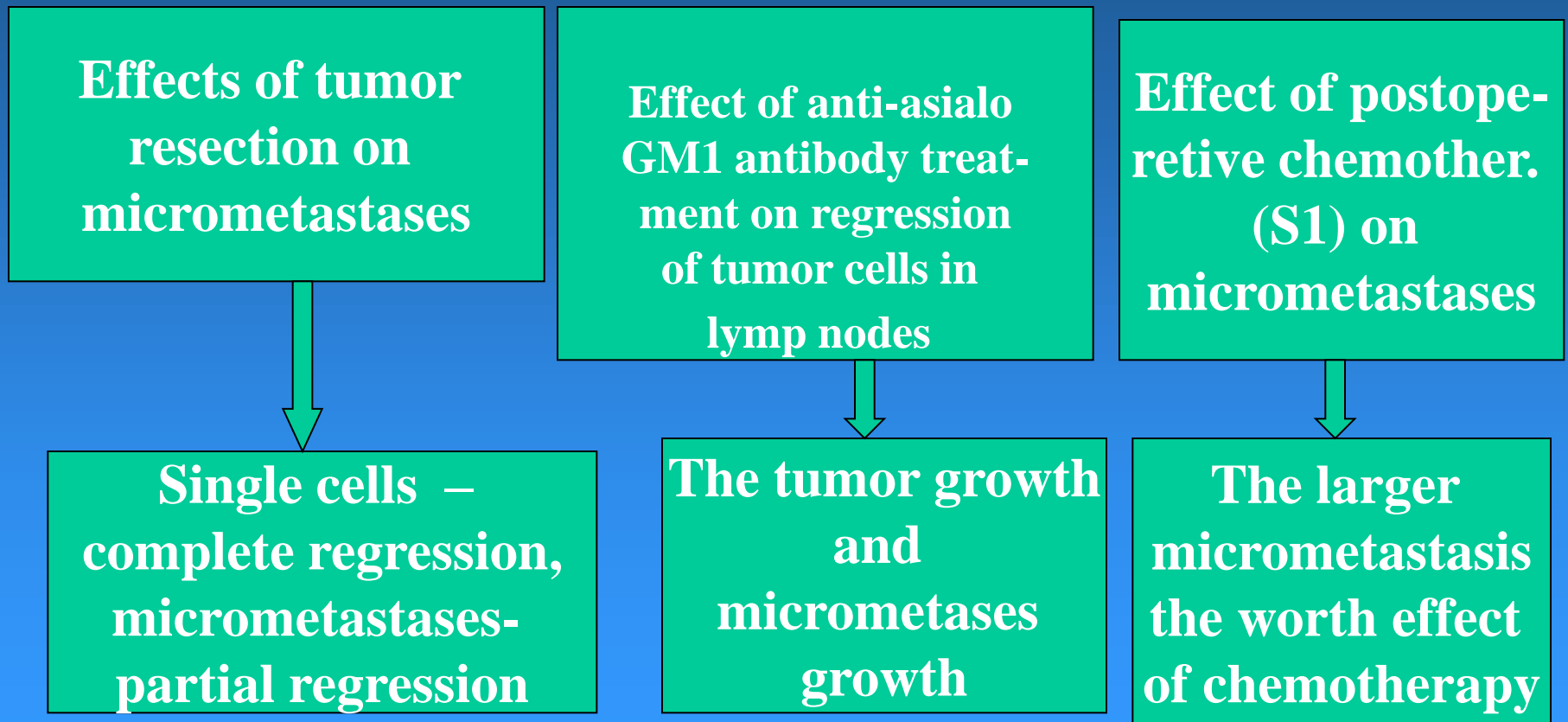
The use of biological model – human gastric cancer cells labeled with fluorescent protein (green fluorescent protein gene – GCIY-EGFP)



Single tumor cells and micrometastases in lymph nodes – biological significance.



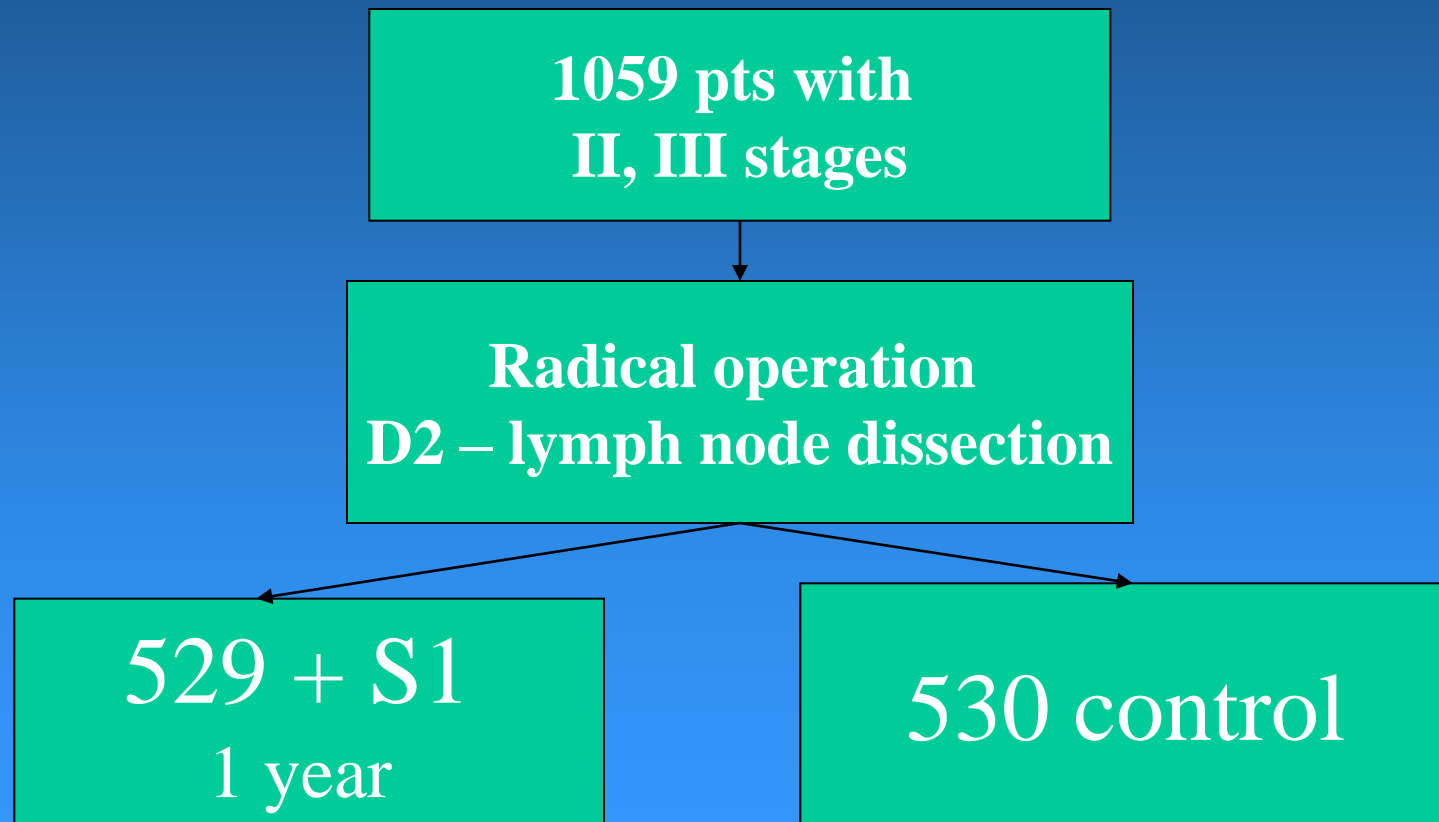
Single tumor cells and micrometastases in lymph node – biological significance.



Micrometastasis in stomach cancer— to watch or to treat?

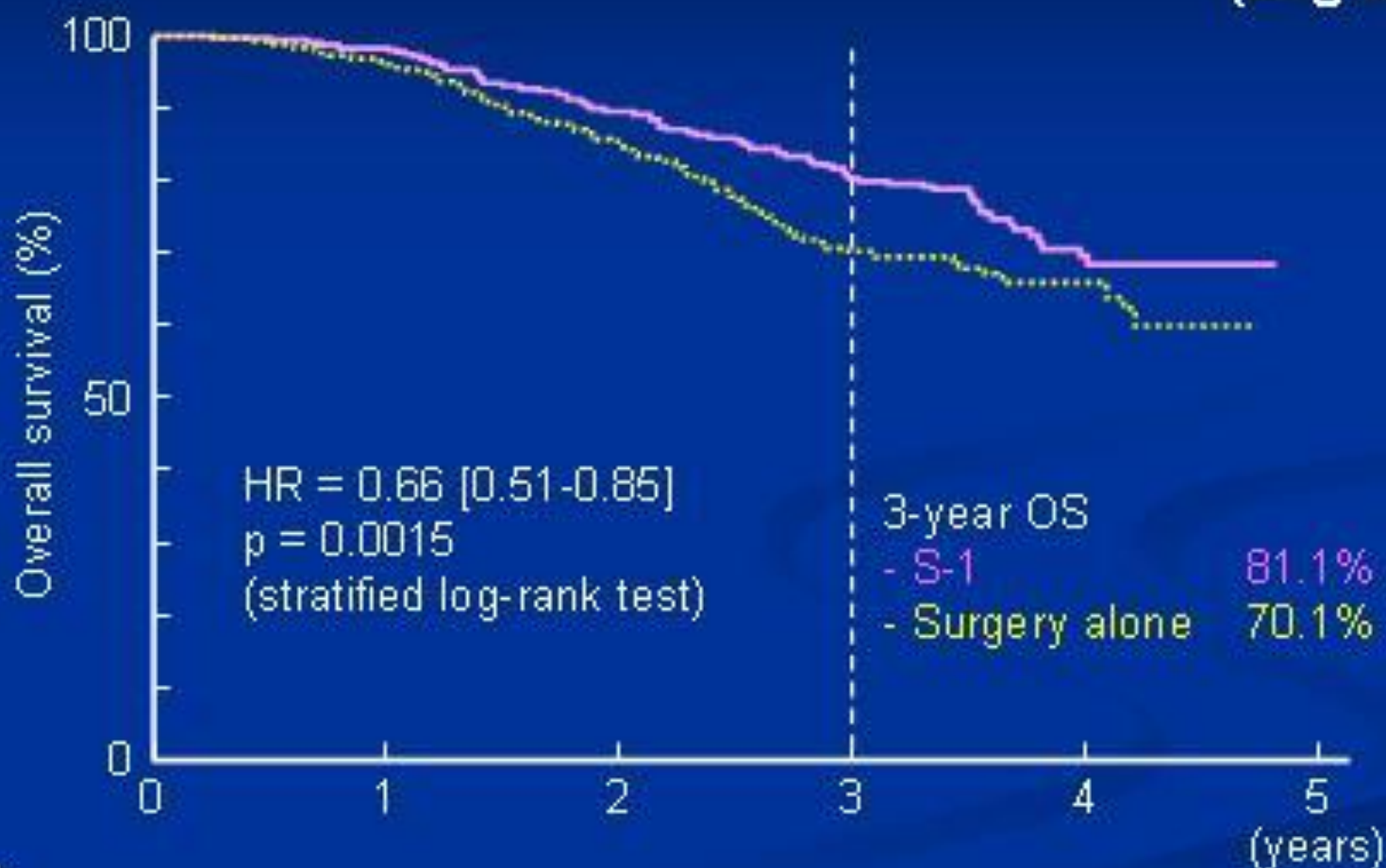


Randomized phase III trial comparing S-1 monotherapy versus surgery alone for stage II/III gastric cancer patients (pts) after curative D2 gastrectomy (ACTS-GC study).



Overall survival

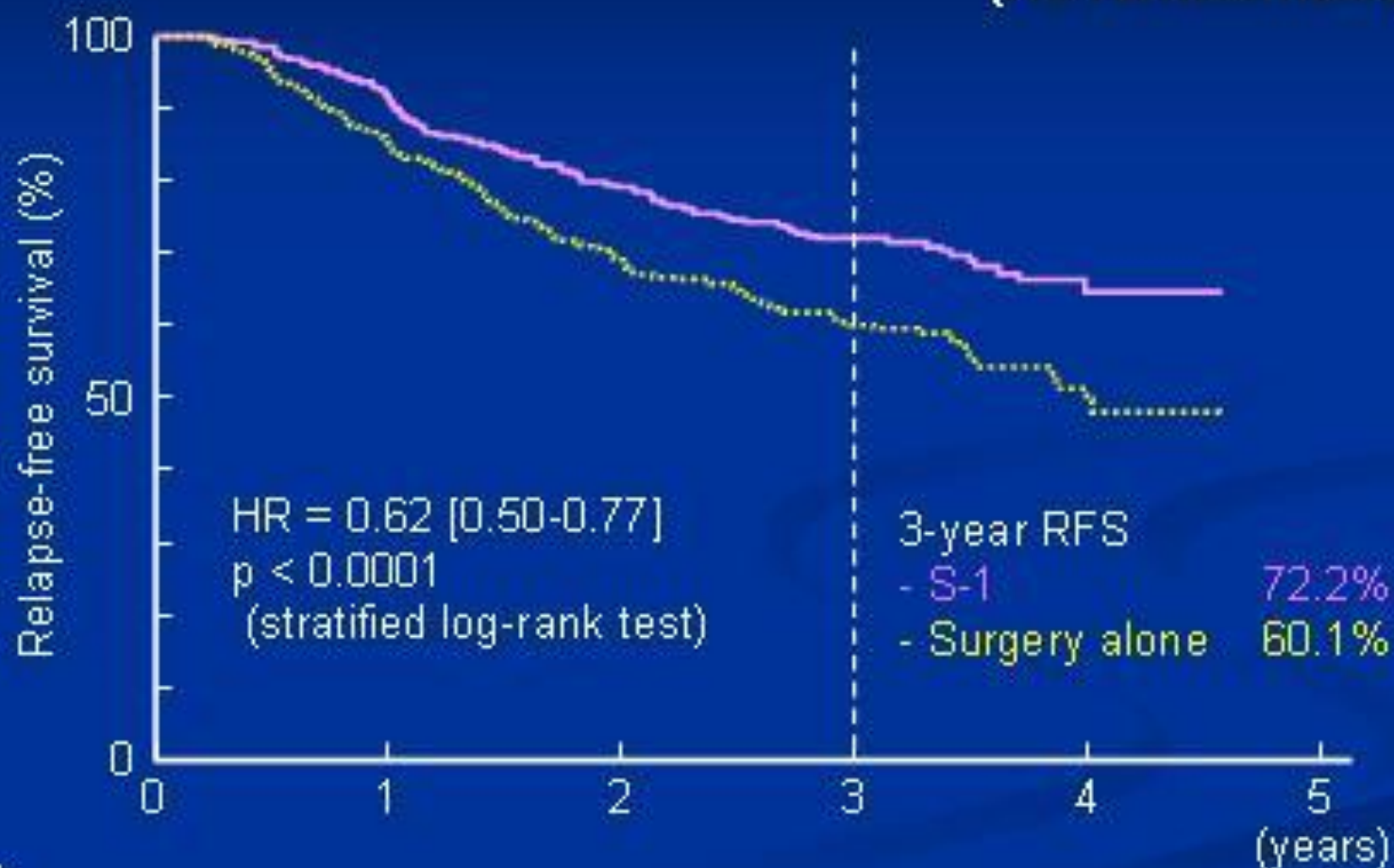
(Eligible)



No. at risk	0	1	2	3	4	5
S-1	515	506	381	201	53	
Surgery alone	519	498	364	172	51	

Relapse-free survival

(All randomized)



HR = 0.62 [0.50-0.77]
p < 0.0001
(stratified log-rank test)

3-year RFS
- S-1 72.2%
- Surgery alone 60.1%

No. at risk	0	1	2	3	4	5
S-1	529	476	322	169	38	
Surgery alone	530	446	285	136	33	

Site of relapse

Site	S-1 (n=529)	Surgery alone (n=530)
No. of relapses	133 (25.1%)	188 (35.5%)
Local	7 (1.3%)	15 (2.8%)
Lymph nodes	27 (5.1%)	46 (8.7%)
Peritoneum	59 (11.2%)	84 (15.8%)
Hematogenous	54 (10.2%)	60 (11.3%)

The search of «targets » on primary tumors and on micrometastasis

- In blood : CD46v6, CEA, MUC1
- In bone marrow: VEGF, HER2, CD31
- In primary tumor: HER2, E-cadherin, MMP-2, VEGF, MMP7, p53
- In lymph nodes : CEA, EMA (anti-MUC1), MUC2
- In peritoneal lavage : CEA, MMP7

Thank you for
attention