In observing the benefits of subgroup analysis from the Pacagnella study, Jacobs (136) reiterated the fact that patients were stratified into inoperable subjects and operable subjects. Jacobs wrote, "these exciting results come from a subgroup analysis of inoperable patients in a trial which included operable patients and which, as a whole, only demonstrated a statistically significant decrease in distant metastases."

Jacobs further implied that this type of discovery, which took advantage of subgroup analysis, could result in a change in standard for therapy of head and neck cancer, "[a]s the authors acknowledge, this trial alone would not be grounds for changing standard treatment, but it lends support to the conclusion that chemotherapy can improve results from radiotherapy in patients with unresectable cancers."

f. Subgroup analysis can justify increases in drug dose for specific subgroups

The clinical trial of gastrointestinal cancer, Van Glabbeke et al. (137) defined several subgroups, including:

- Age;
- Gender;
- Primary site of disease (abdominal, stomach, small bowel);
- Prior treatments for gastrointestinal cancer (surgery, radiotherapy, and chemotherapy);
- Size of lesions (diameter of the largest lesion) at the time of trial inclusion; and
- Baseline hematologic and biologic parameters (white blood cells, granulocytes, platelets, hemoglobin, creatinine, bilirubin, and albumin).

A goal of the clinical trial was to identify subgroups where the drug was less effective. Low efficacy was evident where, during chemotherapy, tumor size or number increased early on, that is, during the first three months of chemotherapy. The study succeeded in identifying a subgroup where the drug was less effective. This was the subgroup of patients with *high granulocyte count at baseline*. Based on this finding, the authors recommended increasing the amount of dose of the drug (imatinib) for this particular subgroup, as follows. "In particular, imatinib resistance can be delayed by increasing the initial dose in patients with high granulocyte counts" (138).

g. Subgroups determined by an analysis of gene expression by microarray analysis

Expression of a collection of genes can be used to define subgroups. A device called a microarray can be used for assaying expression of any number of genes, where

[136] Jacobs C. Head and neck cancer in 1994: a change in the standard of care. *J Natl Cancer Inst*. 1994;86:250–252.

[137] Van Glabbeke M, Verweij J, Casali PG, et al. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: a European Organisation for Research and Treatment of Cancer-Italian Sarcoma Group-Australasian Gastrointestinal Trials Group study. *J Clin Oncol*. 2005;23:5795–5804.

[138] Van Glabbeke M, Verweij J, Casali PG, et al. Initial and late resistance to imatinib in advanced gastrointestinal stromal tumors are predicted by different prognostic factors: a European Organisation for Research and Treatment of Cancer-Italian Sarcoma Group-Australasian Gastrointestinal Trials Group study. *J Clin Oncol*. 2005;23:5795–5804.