Molecular profiling identifies genetic heterogeneity in synchronous and asynchronous breast cancers

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Abstract

Background: Heterologous heterogeneity of tumors is well documented; however, the molecular heterogeneity is not well understood, especially related to driver mutations within clonal populations and their prognostic and predictive value.

Methods: Molecular profiling of breast cancers (BCs) at a single institution were analyzed for differences in clonal populations within the same breast, bilateral synchronous BCs, and/or within primary and paired locally recurrent or metastatic tumors. Gene alterations (GAs) were identified by next generation sequencing (NGS), GAS were compared in 9 synchronous BCs and 48 primary/recurrent paired BCs. Estrogen receptor (ER), progesterone receptor (PR), androgen receptor (AR), were evaluated by immunohistochemistry (IHC). HER2 was evaluated by IHC and in situ hybridization (ISH).

Results: We identified GAs in 10 of 56 cases (18%); T2 were bilateral and 8 were paired primary/recurrent BCs. The 10 cases included 1 pair of separate primaries, 2 primary/locally recurrent, 2 primary/metastatic, 3 metastatic BCs and 2 locally recurrent pairs. In the entire cohort, ER, PR, and HER2 status differed in 9 cases (16%), while AR status differed only in 4 (7%). 23% (13/56) were negative for ER, PR, and HER2 (triple negative (TN)); of 7 TN BCs with GAs in BCs, 6 of 7 (86%) were TN on both samples in the pair. TP53 GAs were identified in 5 of the 10 cases (including the 2 synchronous), PTEN GAs were identified in 3 (1 synchronous), and Pten IHC was evaluated by IHC. Metastatic BCs were included in 3 (1 synchronous), and Pten IHC was evaluated by IHC.

Conclusions: We identified that common GAs differ in both synchronous primary BCs and in paired primary/metastatic tissues and could influence treatment recommendations. These findings highlight the molecular evolution of BC and the importance of evaluating predictive markers of treatment benefit both in synchronous and metastatic BCs.

Table 1. Timing of profile and PTEN IHC Information listed by case of specimen profiled, time between specimen collections, and other associated information.

Table 2. Details of changes in mutation and PTEN IHC

Figure 1. Distribution of cases by ER, PR, HER2 status

Figure 2. Frequency of mutations. Shown by gene for paired samples.