The majority of cancer-associated deaths result from distant organ metastases rather than primary tumors, yet few therapies exist to treat this stage of disease. Recent advances in tumor immunotherapies, such as immune checkpoint blockade, have shown promise for patients with metastatic disease, yet most patients remain unresponsive to these treatments. Here, we investigate the roles of systemic immunity in metastatic progression and response to immunotherapies. We demonstrate that lymph node colonization plays a critical role in metastatic progression by imparting tumor-specific immune tolerance within the immune repertoire of the involved lymph nodes. This tolerance becomes systemic across the host and facilitates metastatic seeding of distant sites. Furthermore, using mouse models and systems approaches, we demonstrate that the generation of effective anti-tumor immune responses to immunotherapies requires activation of immunity in secondary lymphoid organs. Together, these findings demonstrate the critical roles of lymph nodes in facilitating metastatic progression and driving responses to immunotherapy.